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## Description

This invention relates to novel S-nitrosothiol derivatives which are useful as medicines, especially as therapeutics for the cardiovascular diseases such as hypertension and angina pectoris.

Along with aging of society, hypertension and heart diseases have become matters of primary concern, and various cardiovascular medicines have been developed for the treatment of such diseases. There are prior art documents disclosing the production of some nitro-compounds and nitrites among the medicines [Journal of Pharmacy and Pharmacology, 31, 801 (1979)].

In the social circumstances described above, more reasonable agents are being required to be developed in the field of cardiovascular drugs, particularly antihypertensives and therapeutics for angina pectoris. However, satisfactory compounds have not yet been found. There have been no report so far for the application of S-nitrosothiol derivatives as therapeutics for angina pectoris.

#### **DETAILED DESCRIPTION**

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As a result of the research to find out useful compounds as therapeutics for cardiovascular diseases, especially as anti-hypertensives and therapeutics for angina pectoris, the present inventors have found that the compounds represented by the formula (1):

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$$\frac{X_{s}}{X_{t}-N}>CH-\frac{C}{C}-2NO \qquad (1)$$

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wherein  $R^1$  and  $R^2$  represent respectively a hydrogen atom or a hydrocarbon residue which may be substituted;  $R^3$  is a hydrogen atom, an acyl group or a hydrocarbon residue which may be substituted;  $X^1$  is a hydrogen atom, an acyl group, a lower alkoxy group or a hydrocarbon residue which may be substituted;  $X^2$  is an acyl group or a carboxyl group which may be esterified or form an amide; and when  $X^2$  is a carboxyl group  $X^1$  is not a hydrogen atom or acetyl group, and when both  $R^1$  and  $R^2$  are hydrogen atoms  $X^1$  is not acetyl group or gamma-glutamyl group, and the salts thereof are excellent in alleviation of the cardiovascular diseases, and have completed the present invention.

The "hydrocarbon residues" in the above-mentioned "hydrocarbon residues which may be substituted" in the formula (I) include, chain-, cyclic-, saturated-, and unsaturated-hydrocarbon residues, and various combinations thereof. Chain-hydrocarbon residues include straight chain and branched alkyl groups each having 1 to 6 carbon atoms (e.g. methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, tert-butyl, n-pentyl, n-hexyl).

Chain unsaturated hydrocarbon residues include straight chain and branched  $C_{2-4}$ -alkenyl (e.g. vinyl, allyl, 2-butenyl), and  $C_{2-4}$ -alkynyl (e.g. propargyl, 2-butynyl).

Cyclic saturated hydrocarbon residues include monocyclic cycloalkyl having 3 to 7 carbon atoms (e.g. cyclobutyl, cyclopentyl, cyclohexyl), and bridged cyclic saturated hydrocarbon residues having 8 to 14 carbon atoms (e.g. bicyclo[3,2,1]oct-2-yl, bicyclo[3,3,1]nonan-2-yl). Cyclic unsaturated hydrocarbon residues include phenyl and naphthyl groups.

 $R^1$  and  $R^2$  may be bound with each other to form a ring of  $-(CH_2)_{n^2}$  wherein n is an integer of 2 to 6.

Substituents for these hydrocarbon residues include halogen atoms (e.g. chlorine, bromine, and iodine atoms), nitro, nitrile, hydroxyl, carboxyl,  $C_{1-4}$ -alkoxy (e.g. methyloxy, ethyloxy, propyloxy, butyloxy, isopropyloxy),  $C_{1-4}$ -alkylthio (e.g. methylthio, ethylthio, propylthio, isopropylthio, butylthio), amino, mono- or di- $C_{1-4}$ -alkyl substituted amino (e.g. methylamino, ethylamino, propylamino, dimethylamino, diethylamino), mono- or di-aralkyl substituted amino (e.g. benzylamino, 2-hydroxyphenylmethylamino), mono-or di-pyridylcarbonyl substituted amino (e.g. 3-pyridylcarbonylamino),  $C_{1-4}$  alkoxycarbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isobutoxycarbonyl), hydroxycarbonyl,  $C_{1-6}$ -alkylcarbonyl (e.g. methylcarbonyl, carbamoyl, ethylcarbonyl, cyclohexylcarbonyl), carbamoyl, mono- or di- $C_{1-4}$ -alkyl-substituted carbamoyl (e.g. methylcarbamoyl, ethylcarbamoyl, propylcarbamoyl, butylcarbamoyl, diethylcarbamoyl, dibutylcarbamoyl), and phenyl, phenoxy, benzoyl, phenoxycarbonyl, phenyl $C_{1-4}$ -alkyl-carbamoyl (e.g. benzylcarbamoyl, phenethylcarbamoyl) and phenylcarbamoyl which may have 1 to 4 substituents [substituents in the respective phenyl group include  $C_{1-4}$ -alkyl group (e.g. methyl, ethyl, propyl, butyl, isopropyl), halogen atom (e.g. chlorine, bromine, iodine atoms), hydroxyl, benzyloxy, amino, mono- or di- $C_{1-4}$ -al-

kyl-substituted amino (e.g. methylamino, ethylamino, propylamino, dimethylamino, diethylamino, methylethylamino), nitro,  $C_{1-4}$ -alkoxycarbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl)].

The appropriate number of the substitutents in each of these hydrocarbon residues is 1 to 3.

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Acyl groups represented by R<sup>3</sup>, X<sup>1</sup>, and X<sup>2</sup> include carboxylic acyl, carbamic acyl, sulfonic acyl, and substituted oxycarboxylic acyl groups, all of which may be substituted. When an acyl group is substituted, the substituents include those for the hydrocarbon residues described above.

Carboxylic acyl groups include C1-8alkylcarbonyl such as formyl, acetyl, propionyl, butyryl, valeryl, hexanoyl, isobutyryl, and isovaleryl (which may be substituted, for example, with amino, 3-carbamoyl-1,4-dihydropyridin-1-yl, 3-carbamoyl-1-pyridyl, or phenoxy; substituted C<sub>1-6</sub>-alkylcarbonyl groups are exemplified by phenoxyacetyl, 4-aminobutyryl, aminomethylcarbonyl, 2-(3-carbamoyl-1,4-dihydropyridin-1-yl)ethylcarbamoyl, and 2-(3-carbamoylpyridin-1-yl)ethylcarbamoyl), C<sub>3-8</sub>cycloalkylcarbonyl such as cyclopentylcarbonyl and cyclohexylcarbonyl, C<sub>3-8</sub>cycloalkyl-C<sub>1-8</sub>alkylcarbonyl such as cyclopentylacetyl, C<sub>2-6</sub>alkenyl or alkynylcarbonyl such as acryloyl, crotonoyl, 2-pentenoyl, 4-pentynoyl, 2-hexenoyl, 3-hexenoyl, and 2,4-hexadienoyl, aryl carbonyl such as benzoyl, and naphthoyl, pyridylcarbonyl such as nicotinoyl, and dihydropyridylcarbonyl [which may be substituted, for example, with C1\_4alkyl (e.g. methyl, ethyl, propyl, butyl), benzyl, methoxycarbonyl, 3nitrophenyl, nitro, or 2-trifluorophenyl; substituted dihydropyridylcarbonyl groups are exemplified by N-C1-4lkyl-1,4-dihydropyridine-3-carbonyl (e.g. N-methyl-1,4-dihydropyridine-3-carbonyl, N-ethyl-1,4-dihydropyridine-3-carbonyl, N-butyl-1,4-dihydropyridine-3-carbonyl), N-benzyl-1,4-dihydropyridine-3-carbonyl, 2,6-dimethyl-5-methoxycarbonyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-ylcarbonyl, and 2,6-dimethyl-5-nitro-4-(2-trifluorophenyl-1,4-dihydropyridine-3-ylcarbonyl], pyridiniumcarbonyl (in which the nitrogen in the pyridine ring is substituted, for example with C<sub>1-4</sub>alkyl (e.g. methyl, ethyl), or benzyl, and exemplified by C<sub>1-4</sub>alkylpyridinium-3-carbonyl (e.g. methylpyridinium-3-carbonyl, ethylpyridinium-3-carbonyl, propylpyridinium-3-carbonyl), and benzylpyridinium-3-carbonyl).

Carbamic acyl groups include carbamoyl, mono- or di- substituted carbamoyl groups. The mono- and disubstituted carbamoyl groups include mono- and di-C<sub>1-4</sub>alkylcarbamoyl such as methylcarbamoyl, ethylcarbamoyl, propylcarbamoyl, butylcarbamoyl, dimethylcarbamoyl, diethylcarbamoyl, and dipropylcarbamoyl, mono- and di-C<sub>3-6</sub>-alkenyl- and alkynylcarbamoyl such as allylcarbamoyl, 3-butenylcarbamoyl, 4-pentenylcarbamoyl, and diallylcarbamoyl, mono- and di-aromatic group carbamoyl such as phenylcarbamoyl, naphthylcarbamoyl, and diphenylcarbamoyl.

Sulfonic acyl groups include inorganic sulfonyl such as sodiumsulfonyl,  $C_{1-6}$ alkylsulfonyl such as methylsulfonyl, ethylsulfonyl, propylsulfonyl, and butylsulfonyl,  $C_{2-6}$ alkenyl- or alkynylsulfonyl such as allylsulfonyl, and 2-methyl-2-propenesulfonyl, and aromatic sulfonyl such as phenylsulfonyl, p-methylphenylsulfonyl, and naphthalenesulfonyl.

Substituted oxycarboxylic acyl groups include  $C_{1\_8}$ alkyloxycarbonyl which may be substituted with halogen (e.g. chlorine, bromine, iodine), cyano, benzyloxy, phenoxy, di $C_{1\_3}$ alkylamino (e.g. dimethylamino, diethylamino, dipropylamino),  $C_{1\_4}$ alkyloxy (e.g. methyloxy, ethyloxy, butyloxy, t-butyloxy),  $C_{1\_3}$ alkylthio (e.g. methylthio, ethylthio, propylthio), 4-(3-nitrophenyl)-2,6-dimethyl-3-methoxycarbonyl-1,4-dihydropyridin-5-ylcarbonylamino or dihydropyridylcarbonylamino (methyloxycarbonyl, ethyloxycarbonyl, n-propyloxycarbonyl, i-propyloxycarbonyl, n-butyloxycarbonyl, sec-butyloxycarbonyl, t-butyloxycarbonyl, n-hexyloxycarbonyl, 2-fluoroethyloxycarbonyl, 2-chloroethyloxycarbonyl, 2,2,2-trichloroethyloxycarbonyl, and 3-methyl-1,4-dihydropyridin-1-ylcarbonylaminomethyloxycarbonyl),  $C_{3\_8}$ cycloalkyloxycarbonyl (which may be substituted, for example, with halogen such as chlorine, bromine, and iodine) such as cyclopentyloxycarbonyl, and cyclohexyloxycarbonyl,  $C_{3\_8}$ cycloalkyl- $C_{1\_8}$ alkyloxycarbonyl, such as cyclopentylmethyloxycarbonyl,  $C_{2\_7}$ alkenyl- or alkynyloxycarbonyl such as allyloxycarbonyl, crotyloxycarbonyl, and 2-pentene-1-oxycarbonyl, aromatic or aromatic-aliphatic oxycarbonyl (which may be substituted, for example, with halogen such as chlorine, bromine and iodine, or nitro) such as phenyloxycarbonyl, benzyloxycarbonyl, and phenethyloxycarbonyl, and quinuclidinyl.

Lower alkoxy groups represented by X¹ include those represented by the formula: -OR⁴ [wherein R⁴ represents an alkyl group having 1 to 6 carbon atoms (e.g. methyl, ethyl, propyl, i-propyl, butyl, tert-butyl, hexyl)].

Esterified carboxyl groups represented by  $X^2$  include those represented by the formula: -CO-OR<sup>5</sup> [wherein R<sup>5</sup> represents a hydrocarbon residue which may be substituted], and the "hydrocarbon residues which may be substituted" represented by R<sup>5</sup> include the groups described above as "the hydrocarbon residues which may be substituted" represented by R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, or X<sup>1</sup>.

Amide-forming carboxyl groups represented by  $X^2$  include those represented by the formula:

wherein R<sup>6</sup> is a hydrogen atom or a hydrocarbon residue which may be substituted, and R<sup>7</sup> is a hydrogen atom or a lower alkyl group. In the formula described above, the "hydrocarbon residues which may be substituted" represented by R<sup>6</sup> include the "hydrocarbon residues which may be substituted" represented by R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>5</sup>, or X<sup>1</sup>, described above, and the lower alkyl groups represented by R<sup>7</sup> include alkyl groups having 1 to 6 carbon atoms each (e.g. methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, tert-butyl, n-pentyl, n-hexyl). In the formula described above, R<sup>6</sup> and R<sup>7</sup> may constitute a cyclic amino group together with the adjacent nitrogen atom, and the cyclic amino groups formed by R<sup>6</sup>, R<sup>7</sup>, and the adjacent nitrogen atom include nitrogen-containing 5- to 7-membered heterocyclic groups, such as the groups represented by the formula:

those represented by the formula:

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and those represented by the formula:

In these formula, s represents 0, 1, or 2, t represents 1, or 2, and R<sup>8</sup> represents a substituent which the cyclic amino group formed by the R<sup>6</sup>, and R<sup>7</sup> may have, or a hydrogen atom; the substituents include alkyl groups having 1 to 3 carbon atoms each (e.g. methyl, ethyl, propyl), oxo, hydroxy, phenyl, benzyl, and amino groups. The groups represented by the formula:

$$(\widehat{\mathbf{A}}) - \mathbf{NII} - \mathbf{C} - \mathbf{C} - \mathbf{C} - \mathbf{C}$$

as X1 when X1 represents an acyl group, and the groups represented by the formula:

$$R^{1}O - C - C - NII - R^{0}$$

as the substituted amino groups when  $X^2$  represents an amide-forming carboxyl group, represent the residues of amino acid derivatives, where the amino acids are not specified. The amino acids may be of D-form or L-form.  $R^s$ ,  $R^{10}$ , and  $R^{11}$  are the same or different, each representing a hydrogen atom or a lower alkyl group

which may be substituted.  $R^9$  and  $R^{10}$  may bind to each other to form a lower alkylene chain represented by the formula:  $-(CH_2)_{m^-}$  (wherein m represents an integer of 2 to 4), and A represents a hydrogen atom, lower alkyl group, or acyl group.

The residues of amino acid derivatives described above include those of derivatives of amino acids such as glycine, alanine, glutamic acid, leucine, isoleucine, phenylalanine, aspartic acid, cysteine, sarcosine, glutamine, asparagine, and proline.

When the compound of the general formula (I) has an asymmetric carbon atom, the compound may be of D-, L- or DL-form, being unaffected by the asymmetry of the group represented by X¹ or X².

Among the compounds represented by the formula (I) described above, those excellent in chemical stability are desirable, and  $R^1$  and  $R^2$  may be any group that has a steric effect contributing to stabilization of -SNO group, being desirably a  $C_{1-6}$ alkyl group such as methyl, ethyl, or propyl, phenyl, or naphthyl; when  $R^1$  and  $R^2$  are bound to each other, the group formed by  $R^1$  and  $R^2$  together with the carbon atoms to which the groups are bound is desirably cyclopentyl or cyclohexyl.

 $R^3$  is desirably a hydrogen atom, or a  $C_{8-10}$ aromatic acyl group such as benzoyl, naphthoyl, or phenylacetyl.  $X^1$  is desirably a hydrogen atom or an amino acid residue, and the amino acid is desirably glycine, aspartic acid, phenylalanine, asparagine, glutamic acid, or glutamine.  $X^2$  is desirably carboxyl, carbonylamino, or carboxyl forming an amide with an amino acid residue, and the amino acid is desirably glycine, asparagine, glutamine, aspartic acid, glutamic acid, or phenylalanine.

Among the compounds represented by the formula (I) described above, are desirable those wherein each of R¹ and R² represents  $C_{1-8}$ alkyl group, phenyl, or naphthyl, or R¹ and R² form cyclopentyl or cyclohexyl together with the carbon atoms to which R¹ and R² are bound, R³ is a hydrogen atom or a  $C_{8-10}$  aromatic acyl group, X¹ is a hydrogen atom or an amino acid residue of which amino acid is selected from the group consisting of glycine, aspartic acid, phenylalanine, asparagine, glutamic acid, and glutamine, X² is a carboxyl group, carbonylamino or a carboxyl group forming an amide with an amino acid residue of which amino acid is selected from the group consisting of glycine, aspartic acid, asparagine, glutamic acid, glutamine, and phenylalanine.

When the compound (I) of this invention is basic, the compound may form an acid adduct, especially a physiologically acceptable acid adduct; such adducts are exemplified by salts with inorganic acids (e.g. hydrochloric acid, nitric acid, phosphoric acid, hydrobromic acid), and salts with organic acids (e.g. acetic acid, propionic acid, fumaric acid, maleic acid, tartaric acid, citric acid, malic acid, oxalic acid, benzoic acid, methanesulfonic acid, benzenesulfonic acid).

The compounds of the general formula (I) can be produced by nitrosation of the compounds represented by the general formula (II).

$$X_{1} - \frac{X_{2}}{K_{1}} \subset H - \frac{C}{C} - SH \qquad ( \square )$$

wherein R1, R2, R3, X1, and X2 mean the same as described above.

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Reagents generally used for the nitrosation of the compound (II) include nitrogen monoxide, nitrogen dioxide, dinitrogen tetraoxide, nitrosyl chloride, nitrous acid, and ethyl nitrite, but the reagents are not limited to these, and any reagent that can usually be used for nitrosation may be used.

The reaction may be conducted without any solvent or in a solvent. Any solvent may be used as far as it does not inhibit nitrosation, including water, alcohols (e.g. methanol, ethanol, propanol, butanol, tert-butanol), petroleum-composing solvents (e.g. n-hexane, n-pentane, n-heptane), aromatic solvents (e.g. benzene, toluene, pyridine), ethers (e.g. ethyl ether, tetrahydrofuran, dioxane, isopropyl ether), amides (e.g. N,N-dimethylformamide, N,N-dimethylacetamide), esters (e.g. methyl acetate, ethyl acetate, butyl acetate), halogenated hydrocarbons (e.g. dichloromethane, chloroform, dichloroethane, carbon tetrachloride), and dimethyl sulfoxide.

The reaction can be conducted at -30°C to 150°C, but is desirably conducted at a lower temperature (-5°C to 30°C). For one mole of the compound (II), desirably 1 to 5 moles of the nitrosating reagent are used. The reaction time varies depending on the properties of the compound (II) being generally 1 minute to 6 hours, desirably as short as 1 minute to 30 minutes.

The compounds (II) can be produced according to the <u>per se</u> known method [Angewandte Chemie, <u>87</u>, 372 (1975)], for example, by the procedures shown as the Reaction Formulas 1 to 4.

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$$R^{1} = \frac{R^{1} - CHO}{R^{2}} + \frac{CHO}{C} + \frac{CHO}{C$$

wherein the symbols are the same as described above.

# Reaction Formula 1

wherein R' is a  $C_{1-\delta}$  lower alkyl or benzy, and other symbols are the same as described above.

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## Reaction Formula 2

$$\frac{R^{1} \stackrel{Br}{\downarrow} C - CHO}{R^{2} \stackrel{R^{1}}{\downarrow} C - CHO} = \frac{R^{1} \stackrel{SH}{\downarrow} C - CHO}{R^{2} \stackrel{R^{1}}{\downarrow} C - CHO}$$

$$\frac{HCN}{R^{2} \stackrel{R^{1}}{\downarrow} C - CHO} \stackrel{NH_{3}}{\longrightarrow} \frac{R^{1} \stackrel{SH}{\downarrow} C - CHO}{R^{2} \stackrel{NH_{3}}{\longrightarrow} R^{2} \stackrel{R^{1}}{\downarrow} C - CHO}$$

$$\frac{HCN}{R^{2} \stackrel{R^{1}}{\downarrow} C - CHO} \stackrel{NH_{3}}{\longrightarrow} \frac{R^{1} \stackrel{SH}{\downarrow} C - CHO}{R^{2} \stackrel{NH_{3}}{\longrightarrow} R^{2} \stackrel{NH_{3}}{\longrightarrow} R^{2}$$

wherein the symbols are the same as described above.

## Reaction Formula 3

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40 wherein the symbols are the same as described above.

## Reaction Formula 4

The compound (IIa) or (IIb) thus obtained is further subjected to N-acylation, N-alkylation, N-peptide formation, or esterification, alkylation, or peptide formation at the C terminal, to give the compound (II).

These reactions can be conducted according to the per se known method.

The compounds (1) of this invention act on the cardiovascular system of mammals, exerting excellent hypotensive action, anti-arrhythmic action, anti-anginal action, cardiotonic action, or coronary vasodilation.

The compounds (I) of this invention are excellent in duration and strength of the cardiovascular action as

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compared with the known nitro compounds such as nitroglycerine and nitrites, having no or only very mild undesirable side effects in the cardiovascular, psychic-nervous, or digestive system, such as dizziness, palpation, discomfort in the chest, arrhythmia, headache, fatigue, nausea, and vomiting. The compounds are remarkably effective after oral, parenteral, or percutaneous administration. Therefore the compounds are useful as therapeutics or prophylactics for various cardiovascular disorders in mammals including humans. Among the compounds (I) of this invention, those that dilate selectively the coronary vessels are useful as the prophylactics and therapeutics for angina pectoris.

The diseases for which the compounds (I) of this invention are useful include angina pectoris, myocardial infarction, cardiac asthma, achalasia (temporary remission), coronary sclerosis (chronic ischemic heart disease, asymptomatic ischemic heart disease, arteriosclerotic heart disease), maintaining hypotensive state during operation, emergency treatment of abnormal hypertension during operation, acute heart failure, essential hypertension, and renal hypertension; the compounds can be used for prevention and treatment of these diseases.

The compounds of this invention as such or a stabilized conjugate thereof with cyclodextrin, etc. can be administered to mammals including human orally or parenterally in various forms such as tablets, granules, capsules, injections, suppositories, percutaneous preparations, buccal preparations (sublingual tablets), ointments, and cataplasms. The dose varies depending on the type of the disease to be treated and the symptom, the daily dose being generally 0.1 mg to 500 mg, desirably 1 mg to 30 mg for oral administration to an adult human.

In this specification, amino acids, protective groups, and others are sometimes shown by conventionally used abbreviations based on the IUPAC-IUB Commission on Biological Nomenclature. The abbreviations used are listed in the following.

Ac: acetyl

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25 Boc: t-butoxycarbony!

OBzl: benzylester

WSC: 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide

HOBt: 1-hydroxy-benzotriazole

Trt: trity!

30 Pen: penicillamine

Gly: glycine Ala: alanine

Val: valine Leu: leucine

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Phe: phenylalanine Tyr: tyrosine

Glu: glutamic acid
Asp: aspartic acid

The side chains of amino acid residues are represented as follows:

## **EXAMPLES**

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The following Reference Examples, Working Examples, Preparation Examples, and Experimental Examples explain this invention in more detail, but should not limit this invention.

Reference Example 1 (Synthesis of the Compound A-1)

To the solution of S-trityl-L-penicillamine (69.5 g) and di-t-butyldicarbonate (46.5 g) in dichloromethane (1500 ml), was added triethylamine (20.2 ml) at 0°C, and the mixture was stirred at room temperature for 5 hours. To the reaction mixture were added ice and an aqueous solution of potassium hydrogensulfate. The organic layer was washed with an aqueous solution of potassium hydrogensulfate, water, and saturated saline, in this order, and dried over magnesium sulfate. The solvent was evaporated off under reduced pressure, to give N-t-butoxycarbonyl-S-trityl-L-penicillamine (87.0 g).

In the same way the Compound A-2 listed in Table 1 described below was synthesized.

Reference Example 2 (Synthesis of the Compound B-1)

To the solution of N-t-butoxycarbonyl-S-trityl-D-penicillamine (A-2) (6.0 g) in dimethylformamide (40 ml), were added methyl iodide (1.5 ml) and potassium hydrogencarbonate (2.4 g), and the mixture was stirred for 14 hours. To the reaction mixture was added ice-water, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and then with saturated saline, and dried over magnesium sulfate. The solvent was evaporated off under reduced pressure, to give N-t-butoxycarbonyl-S-trityl-D-penicillamine methyl ester (6.0 g).

Reference Example 3 (Synthesis of the Compound B-2)

To the solution of N-t-butoxycarbonyl-S-trityl-L-penicillamine (A-1) (4.0 g) and 1-hydroxy-benzotriazole (abbreviated as HOBt) (1.2 g) in chloroform (40 ml) and tetrahydrofuran (16 ml), was added dropwise by ice-cooling the solution of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (water-soluble carbodiimide: abbreviated as WSC) (1.7 g) in chloroform (10 ml). The mixture was stirred at the same temperature for 1 hour, to which glycine ethyl ester hydrochloride (1.1 g) and triethylamine (0.85 ml) were added, and the mixture was stirred at room temperature for 12 hours. After addition of water, the organic layer was washed with an aqueous solution of potassium hydrogensulfate, water, an aqueous solution of sodium hydrogencarbonate, water and saturated saline, in this order, and dried over magnesium sulfate. The solvent was evaporated off under reduced pressure, and the residue was subjected to column chromatography, to give N-t-butoxycarbonyl-S-trityl-L-penicillamylglycine ethyl ester (4.5 g).

In the same way the Compounds B-3 to B-22 and D-30 listed in Table 1 described below were synthesized.

Reference Example 4 (Synthesis of the Compound C-2)

To the solution of N-t-butoxycarbonyl-S-trityl-L-penicillamylglycine ethyl ester (B-2) (4.5 g) and 2,6-lutidine (2.8 ml) in dichloromethane (100 ml), was added dropwise at 0°C the solution of trimethylsilyl trifluorometha-

nesulfonate (3.9 ml), and the mixture was stirred for 1 hour while the temperature was gradually returned to room temperature. To the reaction mixture was added ice-water, and the organic layer was washed with 1N-hydrochloric acid, water, an aqueous solution of sodium hydrogencarbonate, water, and saturated saline, in this order, and dried over magnesium sulfate. The solvent was evaporated off under reduced pressure, to give S-trityl-L-penicillamylglycine ethyl ester (3.8 g)

In the same way the Compounds C-1, and C-3 to C-22 listed in Table 1 described below were synthesized.

Reference Example 5 (Synthesis of the Compound D-3)

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To the solution of S-trityl-L-penicillamylglycine ethyl ester (C-2) (3.7 g) in dichloromethane (50 ml) were added acetyl chloride (0.66 ml) and triethylamine (0.88 ml) at 0°C. The mixture was stirred at the same temperature for 15 minutes and then ice water was added. The organic layer was washed with an aqueous potassium hydrogensulfate solution, water, an aqueous sodium hydrogencarbonate solution, water and saturated saline, in this order, and dried over magnesium sulfate. The solvent was evaporated off under reduced pressure, and the residue was subjected to silica gel column chromatography, to give N-acetyl-S-trityl-L-penicillamylglycine ethyl ester (3.5 g).

Reference Example 6 (Synthesis of the Compound D-4)

To the solution of S-trityl-L-penicillamylglycine ethyl ester (C-2) (5.4 g) and N-t-butoxycarbonyl-L-glutamic acid- $\alpha$ -benzyl ester (3.8 g) in chloroform (100 ml) was added WSC (2.4 g) at 0°C, and the mixture was stirred at room temperature for 3 hours. To the reaction mixture was added ice water. The organic layer was washed with an aqueous potassium hydrogensulfate solution, water, aqueous sodium hydrogencarbonate solution, water and saturated saline, in this order, and dried over magnesium sulfate. The solvent was evaporated off under reduced pressure, and the residue was subjected to column chromatography, to give (4S)-4-t-butoxycarbonylamino-4-benzyloxycarbonylbutyryl-S-trityl-L-penicillamylglycine ethyl ester (8.4 g).

In the same way the Compounds D-1, D-2, D-5 to D-27 and D-29 listed in Table 1 described below were synthesized.

Reference Example 7 (Synthesis of the Compound E-5)

To the solution of (4S)-4-t-butoxycarbonylamino-4-benzyloxycarbonylbutyryl-S-trityl-L-penicillamylgly-cine ethyl ester (D-4) (8.4 g) in tetrahydrofuran (150 ml) was added 1N-sodium hydroxide (25.3 ml) and the mixture was stirred at room temperature for 2 hours. Tetrahydrofuran was evaporated off under reduced pressure, and the aqueous layer was washed twice with diethyl ether, to which an aqueous potassium hydrogensulfate solution was added to make it acidic, and the solution was extracted with ethyl acetate. The organic layer was washed with water and saturated saline, and the solvent was evaporated off under reduced pressure, to give [N- $\gamma$ -(N-t-butoxycarbonyl)-L-glutamyl-S-trityl-L-penicillamyl]glycine (7.0 g).

In the same way the Compounds E-1 to E-4, and E-6 to E-32 listed in Table 1 described below were synthesized.

Reference Example 8 (Synthesis of the Compound F-5)

The solution of [N- $\gamma$ -(N-t-butoxycarbonyl)-L-glutamyl-S-trityl-L-penicillamyl]glycine (E-5) (3.0 g) in chloroform (60 ml) was bubbled with hydrogen chloride gas at 0°C for 30 minutes. To the reaction mixture was added diethyl ether, and the crystals were collected by filtration and washed with diethyl ether. The crystals were dried under reduced pressure, to give (N- $\gamma$ -L-glutamyl-L-penicillamyl)glycine hydrochloride (1.7 g).

In the same way the Compounds F-1 to F-4, and F-6 to F-32 listed in Table 1 described below were synthesized.

Reference Example 9 (Synthesis of the Compound B-23)

To the solution of N-t-butoxycarbonyl-S-trityl-L-penicillamine (A-1)(4.0g) and HOBt (1.2g) in chloroform ( $40m\ell$ ) and tetrahydrofuran ( $15m\ell$ ), was added dropwise under ice-cooling the solution of WSC (1.7g) in chloroform ( $10m\ell$ ). The mixture was stirred at the same temperature for 1 hour, to which water was added, and the organic layer was washed with an aqueous solution of potassium hydrogensulfate, water, an aqueous solution of sodium hydrogencarbonate, water and saturated saline, in this order, and dried over magnesium sulfate. The solvent was evaporated off under reduced pressure, to give HOBt ester.

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To the solution of p-sulfophenylalanine (2.0g) in water ( $40m\ell$ ), sodium hydrogencarbonate (2.1g) was added. To this solution, the solution of the HOBt ester synthesized as described above in dioxane ( $40m\ell$ ) was added, followed by addition of tetrabutylammonium hydrogensulfate (3.3g), and the mixture was stirred at room temperature for 1 hour. The solvent was evaporated off under reduced pressure and the residue was extracted with chloroform. The organic layer was washed with an aqueous solution of potassium hydrogensulfate, water and saturated saline, in this order, and dried over magnesium sulfate. The solvent was evaporated off under reduced pressure, to give tetrabutylammonium N-t-butoxycarbonyl-S-trityl-L-penicillamyl-P-sulfophenylalanine (7.5g).

In the same way the Compound D-28 listed in Table 1 described below was synthesized.

Reference Example 10 (Synthesis of the Compound C-23)

To the solution of tetrabutylammonium N-t-butoxycarbonyl-S-trityl-L-penicillamyl-p-sulfophenylalanine (B-23)(7.5g) and 2,6-lutidine (3.8m $\ell$ ) in dichloromethane (100m $\ell$ ), was added dropwise at 0°C the solution of trimethylsylyl trifluoromethanesulfonate (5.5m $\ell$ ), and the mixture was stirred for 1 hour while the temperature was gradually returned to room temperature. The solvent was evaporated off under reduced pressure and the residue was washed with diethyl ether and acetone, in this order, to give S-trityl-L-penicillamyl-p-sulfophenylalanine (3.1g).

Table 1 shows the structure, physical properties, and NMR data of the Compounds A-1 to F-32 synthesized in the Reference Examples.

X - Pen - Y   Molecular   Related   NMR spectra	55		50	45 .	<b>4</b> 0	35	30	25	20	15	10	5
X - Pen-Y  Molecular Related NMR spectra of Pen  X Configuration Y  Z formula Ref. Ex. TMS internal physical physical physical physical amorphous  0	á	ᆏ	•	•								
X - Pen - Y  Molecular Related NMR spectra of Pen				2								
X Configuration Y         Z formula formula properties         Ref. Ex. TMS internal (5, ppm) in C (5, ppm) in C (5, ppm) in C (6, ppm) in C (6			×	1	Y — Y							
1 Boc L OH Trt C2sH33NO4S 1 amorphous 2 Boc D OH Trt C23H33NO4S 1 amorphous 1 Boc D OMe Trt C30H35NO4S 2	lođu	Jnd	X Conf.	igura of Pe	tion Y :n	2	1	Relat	Ex.	spectra interna opm) in		ard
2 Boc D OH Trt C28H39NO4S 1 amorphous 1 Boc D OMe Trt C30H35NO4S 2 amorphous	<u> </u>	Вос	•		НО	Trt	C29H33NO4S		1.07(3H),	1. 13(3H),	1.44(9H)	
2 Boc D OH Trt C23H33NO4S 1 amorphous 1 Boc D OMe Trt C30H35NO4S 2 amorphous 6							amorphous		3.41(111), 3	5. 32(1H),	7.14-7.	~ <del>*</del> *
2 Boc D OH Trt C23H33NO4S 1 amorphous 1 Boc D OMe Trt C30H35NO4S 2 amorphous									(911), 7.50-	-7.70(6H)	, 8. 20(11	
amorphous  1 Boc D OMe Trt CaoHasNO.S 2 amorphous	- 5	Вос		Δ	НО	Trt		-	1.06(3H), 1	1. 12(3H),	1.44(9H)	
1 Boc D OMe Trt CooHosNO.S 2 amorphous							amorphous		3.46(111),4	I. 90(1H),	5.37(1H)	_
1 Boc D OMe Trt CsoHssNO.S 2 amorphous									7.10-7.36(	(9Н), 7.56	1-7.70	
1 Boc D OMe Trt CooHosNO.S 2 amorphous			-	-					(84)			
	B-1	Вос		Q	ОМе	Trt	C30H35NO4S	2	1.02(2H), 1	.07(3H),	1.45(9H)	
7. 10-7. 33(9H), 7. 53-7. 70 (6H)			•				amorphous		3.54(1H), 3	. 36(3H),	5.37(1H)	
(H9)				,				<del></del>	7.10-7.33(	9H), 7.53	-7.70	
					;				(84)			

5																			
10		1. 11(311), 1. 18(311), 1. 25(311),	1. 42(9Н), 3. 22(ІН), 3. 96(2Н),	17(2H), 5.34(1H), 6.20(1H),	7. 14-7. 34(9H), 7. 57-7. 70(6H)	1. 10(3H), 1. 13(3H), 1. 22(3H),	.42(9H), 3.43(1H), 3.95(2H),	14(2H), 5.47(1H), 6.53(1H),	11-7.34(9H), 7.57-7.70(6H)	06(3H), 1.13(3H), 1.24(3H),	. 38(3Н), 1. 43(9Н), 3. 38(1Н),	15(1H), 4. 49(1H), 5. 36(1H),	38(1H), 7.14-7.40(9H),	(	88(3H), 0.92(3H), 1.05(3H),	1.16(3H), 1.42(9H), 2.13(1H),	31(1H), 3.66(3H), 4.47(1H),	33(1H), 6. 34(1H), 7. 15-7. 38	73(6H)
15		:	3. 2.	5. 3,	(9H)		3. 4	5. 4	(9H)		1. 4	<del>1</del> . <del>4</del> .	. 1.	(6H)	9;	1. 4.	3. 6	3. 32	7.7
20		1.11(311),	1.42(9H),	4.17(2H),	7.14-7.34	1. 10(3H),	1. 42(9H),	4.14(2H),	7.11-7.34	1.06(3H),	1.38(3H),	4.15(1H),	6.38(1H),	7.56-7.70(6H)	0.88(3H), (	1.16(3H),	3.31(1H), 3	5.33(1H), 6	(9H), 7. 55-7. 73(6H)
25		3				3				3					က				
30		Caallto N2OsS	amorphous		4	C33H+0N2O5S	amorphous			C3+H+2N2O5S	amorphous				C35H++N2O5S	amorphous			
35		Trt			_	7rt	-			Trt					Trt	<del></del>			
40		Gly-OEt				Gly-OEt				L-Ala-OEt					L-Val-OMe			·	
						Q				J.									
<b>4</b> 5	led)			· · · · · · · · · · · · · · · · · · ·						 	•								-
50	l (continued	Boc				Вос				Boc		•			Вос		•		
	1	· 					· · · · · ·	-1	<del></del>							-			_
55	Table	B - 2				B-3				B-4					B-5				

## Boc   Continued)  ## Boc   D   L-Val-OWe   Trl   CosHNaols   3   0.87(3H), 0.90(3H), 1.05(3H), 1.05(3H), 2.12(1H), 3.20(1H), 3.70(3H), 1.43(9H), 2.12(1H), 3.20(1H), 3.70(3H), 4.48(1H), 3.20(1H), 3.70(3H), 4.48(1H), 7.16-7.38    ## Boc   L   L-Leu-OEU   Trl   CosH.sNaols   3   0.91(6H), 1.02(3H), 1.14(3H), 1.14(3H), 1.14(3H), 7.10    ## Boc   L   L-Pro-OMe   Trl   CosH.sNaols   3   1.12(3H), 1.14(3H), 1.14(3H), 7.10    ## Boc   L   L-Pro-OMe   Trl   CosH.sNaols   3   1.12(3H), 1.14(3H), 1.14(3H), 7.10    ## Boc   L   L-Pro-OMe   Trl   CosH.sNaols   3   1.12(3H), 1.14(3H), 1.16(3H), 3.27(3H), 3.27(3H), 3.27(3H), 3.27(3H), 3.20(1H), 4.10(3H), 3.27(3H), 3.20(3H), 3.20(3H), 3.20(3H), 3.20(3H), 3.20(3H), 4.09(2H), 4.81(1H), 5.29(1H), 4.20(3H), 4.2	55	50		45	40	35	30	25	20	15	10	5
1-6 Boc	Tabl	_	ntinue	d)								
Boc L L-Leu-OEt Trt C3,HisN205S 3 0.  -7 Boc L L-Leu-OEt Trt C3,HisN205S 3 0.  -8 Boc L L-Pro-OMe Trt C3,6HisN205S 3 1.  -9 Boc L L-Phe-OEt Trt C4,0HisN205S 3 1.  -9 Boc L L-Phe-OEt Trt C4,0HisN205S 3 1.  -7 7.  -7 7.	8-6	Вос	•	0	L-Val-OMe	ł	C35H++N2O5	8	(3H),	0.90(3H),	1.05(3H),	
Boc L L-Pro-OMe Trt C3, H4, N205S 3 0.  -8 Boc L L-Pro-OMe Trt C3, H4, N205S 3 1.  -8 Boc L L-Pro-OMe Trt C4, H4, N205S 3 1.  -9 Boc L L-Phe-OEt Trt C4, H4, N205S 3 1.  -9 Boc L L-Phe-OEt Trt C4, H4, N205S 3 1.  -7 7.  -7 7.							amorphous		(3H),	1.43(9H),	2. 12(1H),	
Boc L L-Leu-OEt Trt Corffie N205S 3 0.  -8 Boc L L-Pro-OMe Trt Cosft vos S 3 1.  -9 Boc L L-Phe-OEt Trt Ctoft vos S 3 1.  -9 Boc L L-Phe-OEt Trt Ctoft vos S 3 1.  -9 Boc L L-Phe-OEt Trt Ctoft vos S 3 1.  -7 7.  -7 7.			•						29(1H),	3.70(3H),	4. 48(1H),	
Boc L L-Leu-OEt Trt C <sub>3</sub> 7 I <sub>4</sub> 8N <sub>2</sub> O <sub>5</sub> S 3 0.  amorphous 1.  -8 Boc L L-Pro-OMe Trt C <sub>3</sub> 5H <sub>4</sub> 2N <sub>2</sub> O <sub>5</sub> S 3 1.  amorphous 3.  -9 Boc L L-Phe-OEt Trt C <sub>4</sub> 0H <sub>4</sub> 8N <sub>2</sub> O <sub>5</sub> S 3 1.  -9 G.									5.34(1H),	6.37(1H),	7.16-7.38	
Boc L L-Leu-OEt Trt C37H48N2O5S 3 0.  -8 Boc L L-Pro-OMe Trt C35H42N2O5S 3 1.  -8 Boc L L-Pro-OMe Trt C45H42N2O5S 3 1.  -9 Boc L L-Phe-OEt Trt C40H48N2O5S 3 1.  -9 Boc L L-Phe-OEt Trt C40H48N2O5S 3 1.  -7 7 7.  -9 Boc L L-Phe-OEt Trt C40H48N2O5S 3 1.  -7 7 7.									(9H), 7.58	-7. 68(6H)		
amorphous (3)  -8 Boc L L-Pro-OMe Trt C <sub>3</sub> sH <sub>4</sub> zN <sub>2</sub> O <sub>5</sub> S 3 1.  amorphous 1.  -9 Boc L L-Phe-OEt Trt C <sub>4</sub> oH <sub>4</sub> eN <sub>2</sub> O <sub>5</sub> S 3 1.  amorphous 1.  -9 6.	8-7	Boc			L-Leu-OEt		i	က	0.91(6H),	1.02(3H),	1.14(3H),	
-8 Boc L L-Pro-OMe Trt C <sub>3</sub> sH <sub>4</sub> zN <sub>2</sub> O <sub>5</sub> S 3 1.  amorphous 1.  -9 Boc L L-Phe-OEt Trt C <sub>4</sub> oH <sub>4</sub> eN <sub>2</sub> O <sub>5</sub> S 3 1.  -10 Boc L L-Phe-OEt Trt C <sub>4</sub> oH <sub>4</sub> eN <sub>2</sub> O <sub>5</sub> S 3 1.  -11 amorphous 1.							amorphous		1.22(3H),	1. 42(9H),	1.30-1.80	
-8 Boc L L-Pro-OMe Trt C <sub>3</sub> sH <sub>+2</sub> N <sub>2</sub> O <sub>5</sub> S 3 1.  amorphous 1.  -9 Boc L L-Phe-OEt Trt C <sub>4</sub> oH <sub>+6</sub> N <sub>2</sub> O <sub>5</sub> S 3 1.  amorphous 1.				0			•		(311), 3, 45	(1H), 4.13	1(2H), 4.55	
-8 Boc L L-Pro-OMe Trt C35H42N2O5S 3 1.  amorphous 3.			•						(1H), 5.33	(1H), 6.23	1(1H), 7. 10	ı
-8 Boc L L-Pro-OMe Trt C <sub>3</sub> sH <sub>4</sub> zN <sub>2</sub> O <sub>5</sub> S 3 1.  amorphous 3.  -9 Boc L L-Phe-OEt Trt C <sub>4</sub> oH <sub>4</sub> eN <sub>2</sub> O <sub>5</sub> S 3 1.  amorphous 1.									7.40(9H),	7.50-7.75	(H9)	
Boc L-Phe-OEt Trt C40H48N2O5S 3 1.  amorphous 1.	B-8	Вос			L-Pro-OMe		C35H+2N2O5S	က	1. 12(3H),	1. 14(3H),	1.44(9H),	
-9 Boc L L-Phe-OEt Trt C.oH.eN.2O.5 3 1 amorphous 1							amorphous		1.82-2.32	(4H), 3. 27	-3.66(2H)	
5.  -9 Boc L-Phe-OEt Trt C4.0H4.8N2O5S 3 1. amorphous 1.					-				3.64(3H),	3.97(1H),	4.47(1H),	
-9 Boc L-Phe-OEt Trt C4.0H4.8N2O5S 3 1. amorphous 1.				•		• • • • •				7.12-7.33	(6H),	
-9 Boc 'L L-Phe-OEt Trt C40H48N2O5S 3 1. amorphous 1.										(H9)		
1. 4. 6. 7.	B-9	Вос			L-Phe-OEt	Trt	C40H4BN2O5S	8	1.03(3H),	1.09(3H),	1.16(3H),	
. 09(2H), 4.81(1H), 5. . 29(1H), 7.04-7.38(1. . 52-7.73(6H)							amorphous		1.43(9H),	3.07(2H),	3.20(1H),	
. 29(1H) . 52-7. 7									4.09(2H),	4.81(1H),	5.29(IH),	
7.52-7.73(6H)									. 29(1H)	7.04-7.38	(14H),	
									7. 52-7. 73	(H9)		

Γ										T								-	$\overline{}$
	. (	1),	1),	1),	(911)	1),	23	54	. 13-		Н),	Н),	. 48-		H),	H),	н),		
	Τ,	د. ج.		6.	55-7.64	), 1.24(61	50(411), 3.	15(2H), 4.	38(1H), 7.	67(6H)	), 1. 41(91	), 6. 15(11	34(9H), 7.		, 1. 41	), 4.80(1	, 5	40(19H),	
	1.07	2.98(2H)	4.75(	6.63(2H)	2(10H), 7.	1. 17 (3H)	1.80-2.	9(2H), 4.	(1H), 6.	7.57-7.	1. 15(3H	ა.	7.		, 1. 12(3H	, 2. 94(2H	, 5. 07(2H	, 7. 12-7.	67(6H)
	1.02(3H),	1.44(911),	4.09(2H),	5.87(1H),	7.12-7.3	1.04(3H)	1. 43(9H)	(1H), 4.0	(1H), 5.3	7.34(9H)	0.98(3H)	3.60(1H)	6.41(1H)	7.58(6H)	1.05(3H)	2.85(1H)	5.02(2H)	6.11(1H)	7.56-7.6
	3						က				8				က				
	C+0H+6N2O8S	amorphous					C38H+8N2O7S	amorphous	4		C+2H++N2O3S	m. р. 158. 0-	159.0		C+7 H 50 N 2 07 S	amorphous	4		-
	Trt						Trt		-	<u>-</u>	Trt				Trt				
	L-Tyr-OEt				. , , , , ,	_ OEt	L-Glu-OEt				NHCHPh2		•		-08z1	L-Asp-0B21			
<u> </u>	<u> </u>										د				,_				
ontinued															-				
1 (cc	Вос						Вос				Вос				Вос	, ,			:
Table	8-10						B-11				8-12				B-13	: :			
		1 (continued) Boc L-Tyr-OEt Trt C+0H+6N2O6S 3 1.02(3H), 1.	1 (continued) Boc L-Tyr-OEt Trt C+0H+6N2O6S 3 1.02(3H), 1.07(3H), 1. amorphous 1.44(9H), 2.98(2H), 3.	1 (continued) Boc L-Tyr-OEt Trt C+0H+6N2O8S 3 1.02(3H), 1.07(3H), 1. amorphous 4.09(2H), 4.75(1H), 5.	1 (continued) Boc L. L-Tyr-OEt Trt C.0H.sN2OsS 3 1.02(3H), 1.07(3H), 1. amorphous 1.44(9H), 2.98(2H), 3. 4.09(2H), 4.75(1H), 5. 5.87(1H), 6.63(2H), 6.	1 (continued) Boc L. L-Tyr-OEt Trt C.OH.6N2O8S 3 1.02(3H), 1.07(3H), 1. amorphous 4.09(2H), 4.75(1H), 5. 5.87(1H), 6.63(2H), 6. 7.12-7.32(10H), 7.55-	1 (continued) Boc	1 (continued) Boc L. L-Tyr-OEt Trt C+oH+6N2O8S 3 1.02(3H), 1.07(3H), 1.18 1.44(9H), 2.98(2H), 3.26 4.09(2H), 4.75(1H), 5.39 5.87(1H), 6.63(2H), 6.94 7.12-7.32(10H), 7.55-7. Poc L. L-Glu-OEt Trt C38H+8N2O,S 3 1.43(9H), 1.80-2.50(4H)	1 (continued)  Boc L. L-Tyr-OEt Trt C+oH+6N2O8S 3 1.02(3H), 1.07(3H), 1.18 1.44(9H), 2.98(2H), 3.26 4.09(2H), 4.75(1H), 5.39 5.87(1H), 6.63(2H), 6.94 7.12-7.32(10H), 7.55-7. 1.04(3H), 1.17(3H), 1.24 Boc L. L-Glu-OEt Trt C38H+8N2O7S 3 1.43(9H), 1.80-2.50(4H) (1H), 4.09(2H), 4.15(2H)	1 (continued) Boc L. L-Tyr-OEt Trt C+oH+6N2OaS 3 1.02(3H),1.07(3H),1.18(3H), A.09(2H), 4.75(1H), 5.39(1H), 5.87(1H), 6.63(2H), 6.94(2H), 7.12-7.32(10H),7.55-7.64(6H), Boc L. L-Glu-OEt Trt CoeH+8N2O,S 3 1.43(9H),1.80-2.50(4H),3.23 (1H),4.09(2H),4.15(2H),7.54	1 (continued) Boc L L-Tyr-OEt Trt C+oH+sN2OsS 3 1.02(3H), 1.07(3H), 1.18(3H), amorphous 1.44(9H), 2.98(2H), 3.26(1H), 5.87(1H), 6.63(2H), 6.94(2H), 7.12-7.32(10H), 7.55-7.64(6H), 1.04(3H), 1.17(3H), 1.24(6H), 1.04(3H), 1.80-2.50(4H), 3.23 amorphous (1H), 4.09(2H), 4.15(2H), 4.54 (1H), 5.32(1H), 6.38(1H), 7.13 7.34(9H), 7.57-7.67(6H)	1 (continued)  Boc L. L-Tyr-OEt Trt C.oH.6N2O8S 3 1.02(3H), 1.07(3H), 1.18(3H), amorphous 4.09(2H), 2.98(2H), 3.25(1H), 5.87(1H), 6.94(2H), 7.12-7.32(10H), 7.55-7.64(6H), 7.12-7.32(10H), 7.55-7.64(6H), 1.04(3H), 1.17(3H), 1.24(6H), amorphous C. L. C.Glu-OEt Trt C.osH.8N2O,S 3 1.43(9H), 1.80-2.50(4H), 3.23 Amorphous C. H.), 4.09(2H), 4.15(2H), 4.54 C.OSH, 4.15(2H), 4.15(2H), 4.15(2H), 7.13 C.OSH, 7.77-7.67(6H) C.ONTINGED C. NHCHPh2 Trt C.osH.4N2OsS 3 0.98(3H), 1.15(3H), 1.41(9H), C.OSH.4N2OsS 3 0.98(3H), 1.15(3H), 1.41(9H), C.OSH.4N2OsS 3 0.98(3H), 1.15(3H), 1.41(9H), C.OSH.4N2OsS C.O	1 (continued)  Boc L. L-Tyr-OEt Trt C.oH.6N208S 3 1.02(3H), 1.07(3H), 1.18(3H), 1.14(9H), 2.98(2H), 3.26(1H), 5.87(1H), 6.94(2H), 5.87(1H), 6.63(2H), 6.94(2H), 7.12-7.32(10H), 7.55-7.64(6H), 7.12-7.32(10H), 7.55-7.64(6H), 1.04(3H), 1.17(3H), 1.24(6H), 3 1.43(9H), 1.80-2.50(4H), 3.23 Amorphous C. L. L-Glu-OEt Trt C.seH.eN20,S 3 1.43(9H), 1.80-2.50(4H), 3.23 C. L. AHCHPh, Trt C.zeH.eN20,S 3 0.98(3H), 1.15(3H), 1.41(9H), C.zeH.eN20,S C. L. AHCHPh, C.zeH.eN20,S C. C. AHCHPh, C.zeH.eN20,S C. C. AHCHPh, C.zeH.eN20,S C. C. AHCHPh, C. CzeH.eN20,S C. C. AHCHPh, C. CzeH.eN20,C C. C. AHCHPh, C. CzeH.eN20,S C. C. CHP, CON CHPH, C. CZEH.eN20,S C. C. CHP, C	1 (continued)  Boc L L-Tyr-OEt Trt C.oH.eN20eS 3 1.02(3H), 1.07(3H), 1.18(3H),  Amorphous 1.44(9H), 2.98(2H), 3.26(1H),  5.87(1H), 6.63(2H), 6.39(2H),  7.12-7.32(10H), 7.55-7.64(6H),  7.12-7.32(10H), 7.55-7.64(6H),  8c L L-Glu-OEt Trt C.oH.eN20,S 3 1.43(9H), 1.17(3H), 1.24(6H),  8c L NHCHPh2 Trt C.oH.eN20,S 3 0.98(3H), 1.15(3H), 7.13  8c L NHCHPh2 Trt C.oH.eN20,S 3 0.98(3H), 1.15(3H), 1.41(9H),  159.0 6.41(1H), 7.12-7.34(9H), 7.448	1 (continued)  Boc	1 (continued)  Boc L. L-Tyr-OEt Trt C. oH. 6 N. 20 8 3 1.02(3H), 1.07(3H), 1.18(3H), 3.26(1H), amorphous  Boc L. L-Tyr-OEt Trt C. oft H. oft H	1 (continued)  Boc L L-Tyr-OEt Trt C <sub>4.0</sub> H <sub>4.8</sub> N <sub>2</sub> O <sub>8</sub> S 3 1.02(3H), 1.07(3H), 1.18(3H), amorphous amorphous 4.09(2H), 2.98(2H), 3.26(1H), 5.39(1H), 5.39(1H), 5.39(1H), 5.39(1H), 6.63(2H), 6.34(2H), 7.55-7.64(6H), 7.12-7.32(10H), 7.55-7.64(6H), 7.12-7.32(1H), 6.33(2H), 7.55-7.64(6H), 7.12-7.32(1H), 7.55-7.64(6H), 7.13-7.32(1H), 6.15(1H), 7.13-7.32(1H), 6.15(1H), 7.13-7.32(1H), 6.15(1H), 7.13-7.32(1H), 6.15(1H), 7.13-7.32(1H), 7.13-7.32(1	1 (continued)  Boc L L-Tyrr-OEt Trt C <sub>4.0</sub> H <sub>4.8</sub> N <sub>2</sub> O <sub>6</sub> S 3 1.02(3H), 1.07(3H), 1.18(3H), 1.18(3	1 (continued)  L. L-Tyr-OEt Trt C.oH.eNzOsS 3 1.02(3H), 1.07(3H), 1.18(3H), 1.07(3H), 1.18(3H), 1.07(3H), 1.18(3H), 1.18(3H), 1.18(3H), 2.98(2H), 3.26(1H), 3.26(1H), 4.09(2H), 4.75(1H), 5.36(2H), 5.39(1H), 5.36(2H), 5.36(2H), 5.36(2H), 5.36(2H), 5.36(2H), 5.36(2H), 5.36(2H), 7.55-7.64(6H), 7.12-7.32(10H), 7.55-7.64(6H), 7.12-7.32(10H), 7.55-7.64(6H), 3.23 anorphous  Boc L L NHCHPhz Trt C.z.HN.OsS 3 0.98(3H), 1.15(3H), 1.41(9H), 1.18(3H), 1.41(9H), 1.18(3H), 1.16(3H), 1.

55	50	45		40	35	30	25	20	15	10	5
Table		(continued)	_								{
B-14	Вос	-		L-Met-OEt	Trt	C36 II+6 N2 O5 S2	co	1.06(3H), 1	1. 17(3H), 1. 24(3H),	1.24(311),	
						amorphous	*******	1.43(9H),1	. 25-2. 24	. 43(9H), 1. 25-2. 24(2H), 2. 05(3H),	
		•						2.50(2H), 3	50(2H), 3.22(1H), 4.16(2H),	1.16(2H),	
								4. 61(1H), 5. 31(1H), 6. 40(1H),	. 31(1H),	5.40(111),	-
								7. 15-7. 40(9H), 7. 57-7. 67(6H)	9H), 7.57	-7.67(611)	
8-15	Boc:			L-11e-0Me	Trt	C36H+BN2O5S	3	0.89(6H), 1.03(3H), 1.16(3H),	.03(3H),	1.16(311),	
						amorphous		1. $35-1$ . $52$ (	[2H], 1, 42	35-1. \$2(2H), 1. 42(9H), 1. 86(1H),	<del>-</del>
	٠							3.34(1H),3	34(1H), 3.66(3H), 4.52(1H),	4.52(1H),	
								5.32(1H),6	38(111),	32(1H), 6.38(1H), 7.15-7.42(9H),	
								7.53-7.73(6H)	(H9)	(	
B-16	Вос		Q	NHCHPh2	Trt	C+2H+4N2O3S	B	0.98(3H), 1	98(3H), 1.15(3H), 1.41(9H),	1.41(9H),	
						m. р. 158. 0-		3.60(1H), 5	60(1H), 5.28(1H), 6.15(1H),	6.15(1H),	<u> </u>
						159.0		6, 40(111); 7	40(1H); 7:10-7.40(19H),	(19H),	
								7.48-7.57(6H)	(H9)		
B-17	Вос		Ω	L-Leu-OEt	Trt	C37H48N2O5S	က	0.82-0.91(	(6H), 1.05	82-0.91(6H), 1.05(3H), 1.15(3H),	
						amorphous		1.24(3H), 1	.42(9H),	1. 24(3H), 1. 42(9H), 1. 30-1. 81(3H),	÷ ;
								3.34(1H),4	.14(2H),	34(1H), 4.14(2H), 4.51(1H), 5.33	33
		•	,					(1H), 6. 13(1H), 7. 15-7. 33(9H),	1H), 7. 15	-7.33(9H),	
<del></del>								7.56-7.63(6H)	(H9)		
							-				
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5	4(1H),	3(4H),	6(3H), H)	2(4II), 8-4. 49 ),
10	99(3H), 1. 11(3H), 1. 14(3H), 42(9H), 2. 93-3. 16(2H), 3. 34(1H), 08(2H), 4. 77(1H), 5. 27(1H), 32(1H), 7. 08-7. 33(14H), 54-7. 63(6H)	08(3H), 1. 17(3H), 1. 20(3H), 25(3H), 1. 42(9H), 1. 82-2. 43(4H), 20(1H), 4. 07(2H), 4. 16(2H), 53(1H), 5. 34(1H), 6. 39(1H), 15-7. 36(9H), 7. 56-7. 68(6H)	12(3H), 1. 34(3H), 1. 41(9H), 06(1H), 3. 68-4. 10(2H), 3. 76(3H), 38(1H), 5. 21(1H), 6. 06(1H), 19-7. 38(10H), 7. 63-7. 73(6H)	0. 94(6H), 1. 45(9H), 1. 80-2. 22(4H), 3. 43-3. 91(2H), 3. 70(3H), 4. 38-4. 49 (2H), 5. 43(1H), 7. 10-7. 32(9H), 7. 51-7. 63(6H)
15	1. 11(3H) 2. 93-3. 4. 77(1H) 7. 08-7. (6H)	1. 17(3H), 1. 42(9H), 4. 07(2H), 5. 34(1H), (9H), 7. 56	1. 34 (3F 3. 68-4. 5. 21 (1H (10H), 7	1. 45(9H (2H), 3. (1H), 7. (6H)
20	0. 99(3H), 1. 11 1. 42(9H), 2. 93 4. 08(2H), 4. 77 6. 32(1H), 7. 08 7. 54-7. 63(6H)	1. 08(3H), 1. 17(3H), 1. 1. 25(3H), 1. 3. 20(1H), 4. 07(2H), 4. 4. 53(1H), 5. 34(1H), 6. 7. 15-7. 36(9H), 7. 56-7	1. 12(3H), 1. 2. 06(1H), 3. 4. 38(1H), 5. 7. 19-7. 38(1	0. 94(6H), 1. 48 3. 43-3. 91(2H) (2H), 5. 43(1H) 7. 51-7. 63(6H)
25	က	က	က	က
30	CioHicN2OsS amorphous	C38H48N2O7S amorphous	C3+H40N2O8S amorphous	C35H42N2O5S amorphous
35	Tr.t	+	F-	Trt
40	L-Phe-OEt	_ 0Et L-Glu-0Et	L-Ser-OMe	L-Pro-OMe
		a		۵.
45				
45		Вос	Вос	Вос
55 <u> </u>	8 - 8	B-19	B-20	B-21

				- <del></del>
5				
10		1. 03(3H), 1. 10(3H), 1. 17(3H), 1. 30(3H), 1. 43(9H), 3. 00(2H), 3. 16(1H), 4. 07(2H), 4. 27(2H), 4. 58(2H), 4. 73(1H), 5. 29(1H), 6. 27(1H), 6. 78(2H), 7. 05(2H), 7. 12-7. 30(9H), 7. 55-7. 64(6H)	0. 92(12H), 1. 05(3H), 1. 07(3H) 1. 23-1. 66(16H), 1. 4'3(9H), 3. 02-3. 26(1H), 4. 62-4. 75(1H), 5. 36-5. 45(1H), 6. 37(1H), 7. 10-7. 43(12H), 7. 56-7. 78(8H)	1. 07(3H), 1. 11(3H), 1. 63(2H), 2. 33(1H), 3. 54(3H), 7. 12-7. 32 (9H), 7. 56-7. 68(6H)
15		1), 1. 10(3H 1), 1. 43(9H 1), 4. 07(2H 1), 4. 73(1H 1), 6. 78(2H 30(9H), 7.	0. 92(12H), 1. 05(3H), 1. 07( 1. 23-1. 66(16H), 1. 4'3(9H), 3. 02-3. 26(1H), 4. 62-4. 75( 5. 36-5. 45(1H), 6. 37(1H), 7. 10-7. 43(12H), 7. 56-7. 78	1. 07(3H), 1. 11(3H), 2. 33(1H), 3. 54(3H), (9H), 7. 56-7. 68(6H)
20		1. 03(3H 1. 30(3H 3. 16(1H 4. 58(2H 6. 27(1H 7. 12-7.	0. 92(12 1. 23-1. 3. 02-3. 5. 36-5. 7. 10-7.	1. 07(3H 2. 33(1H (9H), 7.
25		က	6	4
30		C. H. S. N. O. S. amorphous	Cs+H77N3O8S2 amorphous	C25H27NO2S Oily
35			Trt	T L
40	·	CH2COOEt Tyr-OEt	SO3.Bu,N DL-Phe-OH	ОМС
45	d)			٥
50	(continued)	O	U	3
5.5	e -	Вос	Вос	=
55	Table	8-22	B-23	C-1

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5					
10		_ 1	1. 25(3H), 1. 27(3H), 1. 29(3H), 1. 62(2H), 1. 80(1H), 3. 88(2H), 4. 16(2H), 6. 96(1H), 7. 16-7. 37 (9H), 7. 62-7. 73(6H)	23(3H), 1. 24(3H), 1. 26(3H), 30(3H), 1. 62(2H), 1. 78(1H), 14(2H), 4. 39(1H), 6. 84(1H), 15-7. 36(9H), 7. 63-7. 73(6H)	0.84(3H), 0.87(3H), 1.25(3H), 1.26(3H), 1.64(2H), 1.79(1H), 2.10(1H), 3.68(3H), 4.36(1H), 6.80(1H), 7.14-7.34(9H), 7.62-7.73(6H)
15		1. 24(3H), 1. 27(3H), 1. 64(2H), 1. 81(2H), 1. 16(2H), 6. 95(1H), (9H), 7. 63-7. 73(6H)	1. 25(3H), 1. 27(3H), 1. 1. 62(2H), 1. 80(1H), 3. 4. 16(2H), 6. 96(1H), 7. (9H), 7. 62-7. 73(6H)	, 1. 24(3H) , 1. 62(2H) , 4. 39(1H) 6(9H), 7. 0	84(3H), 0. 87(3H), 1. 25 26(3H), 1. 64(2H), 1. 79 10(1H), 3. 68(3H), 4. 36 80(1H), 7. 14-7. 34(9H) 62-7. 73(6H)
20		1. 24(3H), 1. 64(2H), 4. 16(2H), (9H), 7. 61	1. 25(3H), 1. 62(2H), 4. 16(2H), (9H), 7. 62	1. 23(3H) 1. 30(3H) 4. 14(2H) 7. 15-7. 3	0. 84(3H), 0. 87 1. 26(3H), 1. 64 2. 10(1H), 3. 68 6. 80(1H), 7. 14 7. 62-7. 73(6H)
25		4	₹	귝	4
30		C.s.H.s.N.O.S amorphous	C <sub>28</sub> H <sub>32</sub> N <sub>2</sub> O <sub>3</sub> S amorphous	C <sub>29</sub> H <sub>3+</sub> N <sub>2</sub> O <sub>3</sub> S amorphous	CooHosN2OoS amorphous
35		T	٦ ۲	Trt	Trt
40		Gly-0Et	Gly-0Et	L-Ala-OEt	L-Val-OMe
45	1)		۵	٠	_
50	(continued				
				==.	=
55	Table	C-2.	C-3	C - 4	C-5

5					· <u>.</u>											<del> </del>				
		);		<u>`</u>			2.4	H),	49	Н),		2.2	96	05-		,	<u>`</u>		H)	
10		, 1. 24(3H	, 2. 06(1H	, 4. 31(1H	6(911),		3(6H), 1.	), 1.65(2	, 4.36-4.	4-7.35(9					8(6H)	, 1. 19(3H	, 3.00(2H)	, 6. 67 (1H)	9-7.70(61	
15		, 0.86(3H), 1.24(3H)	29(3H), 1.80(1H), 2.06(1H),	09(2H), 3.69(3H), 4.31(1H),	67(1H), 7.16-7.36(9II),	(84)	3.80-1.00(6H), 1.23(6H), 1.24	1-1.73(3H	1.84(1H), 4.12(2H), 4.36-4.49	(1H), 6.73(1H), 7.14-7.35(9H),	(H9)	29(3H), 1. 34(3H), 1. 60-2	[4H], 1.84(2H), 2.61(1H), 2.	2H), 3. 63(3H), 4. 35(1H), 7.	7.50-7.7	08(3H), 1. 18(3H), 1. 19(3H)	58(2H), 1. 62(1H), 3. 00(2H)	11(2H), 4.69(1H), 6.67(1H),	01-7.38(4H), 7.59-7.70(6H)	
20		0.83(3H),	1.29(3H),	2.09(2H),	6.67(1H),	7.64-7.73(6H)	0.80-1.00	(3H), 1. 35	1.84(1H),	(1H), 6.73	7. 61-7. 73(6H)	1. 29(3H),	(4H), 1.84	(2H), 3.63	7.42(9H), 7.50-7.78(6H)	1.08(3H),	1.58(2H),	4.11(2H),	7.01-7.38	
25		4		·			4					7				4				
30		Coollo NoOoS	amorphous				C22H+0N2O3S	amorphous	•			C30 H3+N2O3S	amorphous		1.	C35H38N2O3S	amorphous			
35		Trt					Trt					Trt				Trt				
40		L-Val-OMe					L-Leu-OEt					L-Pro-OMe				L-Phe-OEt				
<b>4</b> 5	3)	O					_					ب.	-			7				
	nuec																			
50	(continued)																-			
	e 1	==					$\equiv$					H				H				
55	Table	9-0					C-7					C-8				6-0				

5					
10		5. 26(9H), 1. 09(3H), 1. 18(6H), 1. 60(2H), 1. 63(1H), 2. 93(2H), 4. 10(2H), 4. 64(1H), 6. 67(1H), 5. 75(2H), 6. 95(2H), 7. 10-7. 38 (9H), 7. 60-7. 70(6H)	23(6H), 1. 24(6H), 1. 64(2H), 84(1H), 1. 80-2. 43(4H), 4. 10 (2H), 4. 14(2H), 4. 42(1H), 6. 98 (1H), 7. 15-7. 36(9H), 7. 63-7. 72 (6H)	20(3H), 1. 21(3H), 1. 62(2H), 97(1H), 6. 07(1H), 7. 10-7. 32 (20H), 7. 60-7. 70(6H)	17(6H), 1. 50(1H), 1. 58(2H), 72(1H), 3. 04(1H), 4. 76(1H), 96-5. 17(4H), 6. 91(1H), 08-7. 44(19H), 7. 55-7. 77(6H)
20		0 1 4 0 0			1. 2. 4.
25		₹*	7	4	4
30		Coelle N2O,SSi amorphous	C33H+0N2OsS amorphous	C37H36N2OS amorphous	C <sub>42</sub> H <sub>+2</sub> N <sub>2</sub> O <sub>5</sub> S amorphous
35		⊢ 1 1	<b>⊢</b>	1 r t	F
40		SiMe <sub>3</sub> L-Tyr-OEt	_ 0Et L-Glu-0Et	NHCHPh <sub>2.</sub>	L-Asp-0Bz1
		·	<b>.</b>		
45	(pa		·		
50	(continued)				
	$\vdash$	=			= .
55	Table	01-2	C-11	C-12	C-13

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5		4(11),	4(2H),										<u>-</u>			(2H),				
10		1(211), 1.8	(3H), 2. 4	7.01(1H)	-7.79(611)	-1.93(3H)	1.61(2H),	4. 41(1H),	(9H),		1. 59(2H),	7.06-7.35	8-7.68(61		1. 25(3H),	(3H), 1.61	4.38(1H),	(9H),		
15		12-1. 34(911), 1. 63(211), 1. 84(111),	20(2H), 2.05(3H), 2.44(2H),	16(2H), 4.52(1H), 7.01(1H),	13-7. 42(911), 7. 56-7. 79(611)	73-0.94(6H), 0.96-1.93(3H),	04(3H), 1.17(3H), 1.61(2H),	79(1H), 3.68(3H), 4.41(1H),	82(1H), 7.14-7.38(9H),	(H9)	21(3H), 1. 22(3H),	96(1H), 6.06(1H), 7.06-7.	(19H), 7. 53(1H), 7. 58-7. 68(6H)		88(6H), 1. 23(3H), 1. 25(3H),	28(3H), 1. 40-1. 74(3H), 1. 61(2H),	88(1H), 4.13(2H), 4.38(1H),	6.81(1H), 7:15-7.37(9H),	(H9)	
20		1. 12-1. 3	1.80-2.2	4.16(2H),	7. 13-7. 4	0.73-0.9	1.04(3H),	1.79(1H),	6.82(1H),	7. 56-7. 74 (6H)	1. 21(3H),	1.96(1H),	(19H), 7.5		0.88(6H),	1.28(3H),	1.88(1H),	6.81(1H),	7. 57-7. 72(6H)	
25		4				4		<del></del>			4				4					
30		C3 , H3 8 N2 03 S2	amorphous			C31H38N2O3S	amorphous				C37 H38 N2OS	amorphous			C32H40N2O3S	amorphous				
35		Tr.				Trt			<del></del>		Trt (				Trt	<del></del>			<del></del>	-
40		L-Met-OEt				L-11e-0Me					NHCHPh2	-			L-Leu-OEt				•	
45	J)		:								Ω				Ω		- <u>-</u>			
	inue															0				
50	(continued		•											-						
		=				=					==				æ					
55	Table	0-14				C-15				-	C-16				C-17					
						1														j

	_				
5			4 II),	2H),	12(4H), 32(2H), H)
10		, 1. 23(3H), , 3. 00(2H), , 6. 88(1H), 67-7. 72(6H)	24(6H), 1. 27(3H), 82(1H), 1. 80-2. 42(4H), 14(2H), 4. 39(1H), 14-7. 36(9H)	(3H), 1. 29(3H), (1H), 3. 61-3. 98(2H), (1H), 6. 79(1H), , 7. 65-7. 74(6H)	1. 60-2. 2. 90-3. (1H), -7. 68(6
15		(3II), 1. 20 (3II) (2H), 1. 71 (1H) (2H), 4. 65 (1H) -7. 36 (14H), 7.		1. 27 (3H) 1. 67 (1H) 4. 50 (1H) (9H), 7.	31(3H 90(1H 25-4. H), 7.
20		1. 17(3H), 1. 20(3H), 1. 2 1. 48(2H), 1. 71(1H), 3. 0 4. 10(2H), 4. 65(1H), 6. 8 7. 00-7. 36(14H), 7. 67-7	1. 23(3H); 1. 24 1. 60(2H), 1. 82 4. 08(2H), 4. 14 6. 97(1H), 7. 14 7. 62-7. 73(6H)	0. 08(9H), 1. 27(3H), 1. 1. 62(2H), 1. 67(1H), 3. 3. 68(3H), 4. 50(1H), 6. 7. 15-7. 37(9H), 7. 65-7	1. 05(3H), 1. 31 1. 82(2H), 2. 90 3. 68(3H), 4. 25 7. 12-7. 34(9H)
25		4	4	4	
30		CasHagN2OaS amorphous	CaaH+oN2OsS oily	C32H40N2O4SSi amorphous	C30H34N2O3S amorphous
35			T 1	Trt	Tr t
40		L-Phe-OEt	_ OEt L-Glu-OEt	Si(Me)	L-Pro-OMe
45		۵	۵ .		۵
73	ued)	•			
50	continued				
	o U	=		<b>E</b>	Ξ .
55	Table	C-18	61-0	0-20	C-21

55		50	45	40	35	30	- 25	15 20	10	5
rable		(continued								
C - 2 2	= '	•		ÇII2COOEt Tyr-OEt	Trt	C39H44N2O6S amorphous	4	1. 09(3H), 1. 18(3H), 1. 20(3H), 1. 31(3H), 1. 55(2H), 1. 64(1H),	H), I. 20(3H), H), I. 64(IH),	
								2. 95(2H), 4. 11(2H), 4. 28(2H), 4. 60(2H), 4. 53-4. 76(1H), 6. 69 6. 82(2H), 7. 01(2H), 7. 07-7. 31	95(2H), 4.11(2H), 4.28(2H), 60(2H), 4.53-4.76(1H), 6.69(1H), 82(2H), 7.01(2H), 7.07-7.31(9H),	~ ~ ~
600			-	:	f			7. 58-7. 69(611)		
87-7	<b>-</b>			SO3H DL-Phe-OH	- -	CaaHa+N2OaS2	01	*0.99(3H), 1.11(3H), 2.09(2H) 2.10(1H), 3.01(2H), 4.39(1H).	3H), 2.09(2H), H).4-39(1H).	
								7, 16-8, 52(2211)		
		-								
,						C+2H+8N2O7S	9	1.01(3H), 1.12(3H), 1.41(9H)	H), 1. 41(9H),	Γ-
0-1	Boc-L-6	Boc-L-Glu-0Bz1	Ω	ОМе	Trt	amorphous		1.70-2.45(4H), 3.65(3H), 3.85	.65(3H), 3.85	
								(1H), 4. 35(1H), 5. 16(2H), 5. 34	.16(2H), 5.34	
								(1H), 6. 54(1H), 7. 13-7. 37(14H)	.13-7.37(14H),	
								7.54-7.62(6H)		
					_	-		1. 02(3H), 1. 13(3H), 1. 44(9H),	II), 1. 44(9II),	
D-2	Boc-D-G1u-0Mc	.lu0Mc	a	ОМе	Trt	C38H4+N2O7S	9	1.70-2.45(4H), 3.68(3H), 3.72	.68(3H), 3.72	
						amorphous		(3H), 3.81(1H), 4.33(1H), 5.29	.33(1H), 5.29	
								(1H), 6. 38(1H), 7. 14-7. 32(9H),	.14-7.32(9H),	
								7.53-7.68(6H)		_

	55	50	45	40	35	30	25	20	15	10	5
able'	Н	(continued)									
0-3	Ac			Gly-OEt	Trt	C30 H3+N2O+S	5	1.11(3H),	1. 15(311),	1. 25(311),	
						amorphous		1.98(3H),	3, 77(111), 3.	3.95(2H),	
	•							4.18(2H),	6. 23-6. 36	23-6.36(2H), 7.16	
								7.35(9H),	7. 58-7. 67	67 (6H)	
		       						1.12(3H),	1.19(	311), 1. 25(311)	
1)-4	Boc-[,-(	Boc-1,-Glu-0Bz1	د۔	Gly-0Et	Trt	C+5H53N3O8S	9	1.41(9H),	41(9H), 1.55-2.26(4H), 3.	(411), 3.57	1
	, , , ,					amorphous		(1H), 3.94	3.94(2H), 4.17	4.17(211), 4.33	<sub></sub>
						ı		(1H), 5.12	5.12(2H), 5.38	38(1H), 6.23	3
		-						(1H), 6.36(1H), 7.	(1H), 7. 14	14-7. 44(1411	( <u>[</u>
					-			7.54-7.76(6H)	(H9)		
								1.13(3H),	13(3H), 1. 17(3H), 1. 21(3H), 1	1. 21(311)	, 1.39
5-5	Boc-1,-(	Boc-1,-Glu-0Bz1	Ω	Gly-OEt	Trt	C+ SH53N3O8S	9	(9H), 1.52	(9H), 1. 52-2. 32(4H), 3. 65	), 3. 65(111)	·,
) )	) , ·							3.91(2H),	91(2H), 4: 12(2H), 4.	, 4. 29(1H), 5.	, 5. 14
				1		•		(2H), 5.46	(2H), 5.46(1H), 6.52(1H), 6.87(1H),	2(1H), 6.8	7(1H),
			-					7.10-7.4	10-7.44(14H), 7.	46-7.76(6H)	(H)
		L						1.12(3H),	12(3H), 1.20(3H), 1.25(3H), 1.42	, 1. 25(3H)	, 1. 42
0-6	Boc-D-	Boc-D-Glu-OMe	Ω	Gly-OEt	Tr	C39H49N3O8S	9	(9H), 1. 48	(9H), 1. 48-2. 36(4H), 3. 63(1H),	), 3, 63(11	.,
) 1	) )							3.68(3H),	68(3H), 3.94(2H), 4.17(2H), 4.30	, 4. 17(2H)	, 4.30
								(IH), 5.3	(1H), 5.34(1H), 6.26(1H), 6.48(1H),	6(1H), 6.	18(1H),
								7.15-7.34(9H), 7.		57-7. 67 (611)	1)

55	50	45	40	35	30	25	10 15 20	5
Table	le 1 (continued)	ed)						
D-7	Boc-L-Glu-		Gly-OEt	Trt	C+sHs3N3O8S	9	1. 12(3H), 1. 15(3H), 1. 24(3H), 1. 40 (9H), 1. 80-2. 20(2H), 2. 35-2. 63	0
					amorphous		(2H), 3. 51(1H), 3. 92(2H), 4. 10(1H)	
							4.15(2H), 5.10(2H), 5.34(1H), 6.34	
							(1H), 6. 94(1H), 7. 14-7. 37(14H),	
							7. 58-7. 67 (611)	
	l_						1. 10(3H), 1. 18(3H), 1. 24(3H), 1. 39	6
D-8	Boc-L-Asp-0Bz1	<u> </u>	Gly-0Et	Trt	C H 1 N 3 0 8 S	9	(9H), 2. 62-2. 96(2H), 3. 51(1H), 3. 90	0 6
					amorphous		(2H), 4. 12(2H), 4. 52(1H), 5. 14(2H),	
							5.74(1H), 6.20-6.35(2H), 7.14-7.35	35
							(14H), 7.56-7.66(6H)	
	·						1. 09(3H), 1. 15(3H), 1. 23(3H), 1. 34	T
D-0	Boc-L-Glu-0B2		L-Ala-OEt	Trt	C+eHssN3O8S	9	(3H), 1. 42(9H), 1. 65-2. 28(4H), 3. 61	=
					amorphous		(1H), 4. 14(2H), 4. 33(1H), 4. 44(1H),	
							5.12(2H), 5.38(1H), 6.24(1H), 6.38	~~
							(IH), 7. 14-7. 44(14H), 7. 58-7. 68(6H)	$\bigcirc$
		•				-	0.85(3H), 0.89(3H), 1.12(3H), 1.21	
D-10	Boc-L-Glu-0Bz]		L-Val-OMe	Trt	C47H57N308S	ဖ	(3H), 1. 42(9H), 1. 70-2. 28(5H),	
					amorphous		3. 39(1H), 3. 65(3H), 4. 36(1H), 4. 41	
							(1H), 5. 09(2H), 5. 46(1H), 6. 19(1H),	
							6. 46(1H), 7. 15-7. 41(14H), 7. 59-	
							7.69(6H)	
								7

		<del></del>									1					
5	II), 1. 15	-	H), 4. 44 1II), 6. 38	14H),		. 18(3H), . 27(7H),	H), 4.44	. 10(1H),	7.58-		H), 1.67	3.40-	93(1H), 4.37	5.36(1H),	7.49-	
10	1, 06(3H),	30-2.37(	), 4. 26(1 H), 5. 37(	15-7, 44(		10(3H), 1 ), 1.30-2	), 4.34(1	40(1H), 6	40(14H),		), 1. 42(9H), 1.	. 20(1H),	(), 3, 93	12(2H),	44(14H),	
15	0 88(3H), L.	9(9H), 1.	3. 68(3H), 3. 76(1H), 4. 26(1H), 4. 44 (1H), 5. 07-5. 23(2H), 5. 37(1H), 6. 38	49(1H), 7.15-7.44(14H), 66(6H)		0.85-0.97(6H), 1.10(3H), 1.18(3H), 1.22(3H), 1.42(9H), 1.30-2.27(7H),	61(1H), 4.11(2H), 4.34(1H), 4.44	(1H), 5.10(2H), 5.40(1H), 6.10(1H),	39(IH), 7. 14-7. 40(14H), 7. 58-		22(3H), 1. 26(3H),	-2.34(8H), 3.06-3.20(1H), 3.40-	3.52(1H), 3.63(3H), 3.	(1H), 4. 42(1H), 5. 12(2H), 5. 36(1H)	6. 42(1H), 7. 10-7. 44(14H), 7. 49-	
20	n 85(3H), 0	(3H), 1. 39(9H), 1. 60-2. 37(5H)	3.68(3H), (1H), 5.0	(1H), 6. 49(1H) 7. 56-7. 66(6H)	-	0.85-0.9 1.22(3H)	3.61(1H)	(1H), 5. 1	6.39(1H)	7.67(6H)	1. 22(3H)	-2.34(8H	3.52(1H)	(1H), 4. 4	6. 42(1H)	7.72(6H)
	_										-	9				
25		9				9					<u> </u>					
30		C+7H57N3O8S	amorphous			C He . N3O & S	m. p. 177.0-	179.0				C+7Hs5N3O8S	amorphous	ı		
35		Trt				← 	<del></del>					Trt				
40		L-Val-OMe 7				9.1-1 13.0-1						L-Pro-OEt				
<b>4</b> 5		۵				_	)					د				
	ned	128	•			R ?						128				
50	1 (continued)	Boc-L-Glu-0Bz1				Rool - 6 111-0182			-			  Boc-L-G u-0Bz				
55	Table	0-11 8				, I - C						D-13				
	Ta 	0					2			•		$\dot{\Box}$	)			ļ

93	55	50	45	40	35	30	25	20	15	10	5
Table	г	(continued)									
D-14	Boc - [.	Boc-L-Glu-0Bz1		l,-Phe-OEt	£	Cs.HssNsOsS amorphous	9	1. 08(3II), 1. 13(3II), 1. (9H), 1. 54-2. 24(4H), 3 3. 39(1H), 4. 12(2H), 4.	08(3II), 1. 13(3II), 1. 26(3II), 1. 42 H), 1. 54-2. 24(4H), 3. 02(2H), 39(1H), 4. 12(2H), 4. 32(1H), 4. 75	1. 26(3II), , 3. 02(2II), 4. 32(1II),	1. 42
								(1H), 5. 12( 6. 38(2H), 7 7. 63(6H)	H), 5. 12(2H), 5. 46(1H), 6. 20-38(2H), 7. 03-7. 38(19H), 7. 5363(6H)	(19II), 6. 20 (19II), 7. 5	53-
0-15		Boc-L-Glu-0Bz1	7	SiMe <sub>3</sub> L-Tyr-OEt	Trt	CssHe,NoOsSSi	9	0.26(9H), 1.0 (9H), 1.58-2.	26(9H), 1.09(3H), 1.15(6H), 1 H), 1.58-2.30(4H), 2.95(2H),	9(3H), 1. 15(6H), 1. 43 30(4H), 2. 95(2H), 3. 33	1. 43
						amorphous		(1H), 4. 06(2H), 4. 33(1H), 4. 70(1H), 5. 12(2H), 5. 49(1H), 6. 23(1H), 6. 32 (1H), 6. 75(2H), 6. 97(2H), 7. 10-7. 40 (14H), 7. 55-7. 65(6H)	2H), 4. 33( . 49(1H), 6 2H), 6. 97( -7. 65(6H)	(1H), 4. 70(1H) 5. 23(1H), 6. 32 (2H), 7. 10-7. 4	(1H), 6.32
D-16		Boc-L-Glu-0Bz1		L-Glu-OEt	Trt	CsoHe, N3O, oS	9	1. 08(3H), 1. 18(3H), 1. 22(3H), 1. (3H), 1. 42(9H), 1. 80-2. 42(8H),	. 18(3H), 1 9H), 1.80-	22(3H), -2. 42(8H)	1. 26
	•					m. p. 167. 0- 168. 5		3. 49(1H), 4. 10(2H), 4. 12(2H), 4. 34 (1H), 4. 48(1H), 5. 11(2H), 5. 41(1H),	49(1H), 4. 10(2H), 4. 12(2H), 4. 34 H), 4. 48(1H), 5. 11(2H), 5. 41(1H)	12(2H), (2H), 5. 41	4.34 (1H),
								6. 30(1H), 6. 40(1H), 7 (14H), 7. 57-7. 69(6H)	30(1H), 6. 40(1H), 7. 4H), 7. 57-7. 69(6H)	. 15-7. 37	

				· · · · · · · · · · · · · · · · · · ·
5		(9II), 1. 68 1(LII), (1II), 6. 28 II), 7. 50-	H), (2H), H), . 25(1H),	1. 21(3H), 1. 23(3H), 1. 72-2. 28(6H), 2. 05(3H), 3. 38(1H), 4. 15(2H), 4. 56(1H), 4. 97-5. 23(2H), 6. 25(1H), 6. 39(1H), (14H), 7. 58-7. 67(6H)
10		), 1. 41(9 H), 4. 31( ), 6. 09(1 . 36(24H)	19(3H), 1. 41(9H), H), 2. 72-3. 12(2H) 32(1H), 4. 80(1H), H), 5. 43(1H), 6. 25 03-7. 44(24H), H)	(3H), 1. 23(3H), -2. 28(6H), 2. 05 (1H), 4. 15(2H), (1H), 4. 97-5. 23 (1H), 6. 39(1H), ), 7. 58-7. 67(6H)
15		2. 23(4II), 3. 89(1II), 4. 31(1II), 1. 6. 2 (23(4II)), 5. 36(1II), 6. 09(1II), 6. 2 (24II), 7. 10-7. 36(24II), 7. 50-58(6II)	\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\	
20		1. 07(3H) -2. 23(4H) 5. 10(2H) -6. 43(2H) 7. 58(6H)	1. 07(3H), 1. 15 1. 70-2. 27(4H) 2. 96(1H), 4. 32 4. 94-5. 22(6H) 6. 52(1H), 7. 03 7. 56-7. 64(6H)	1. 11(3H), 1. 43(9H), 2. 47(2H), 4. 34(1H), 5. 42(1H), 7. 14-7. 37
		9	9	9
25		S M	လွ	
		N <sub>3</sub> O <sub>6</sub>	NaO.	N <sub>3</sub> O <sub>8</sub> . 1.5- 3.0
30		Cs.Hs7NaOgS amorphous	CssHs3N3O10S amorphous	C <sub>+8</sub> H <sub>59</sub> N <sub>3</sub> O <sub>8</sub> S <sub>2</sub> m. p. 161. 5- 163. 0
35		Tr t	F-	₩ ₩
40		NHCHPh <sub>2</sub>	L-Asp-0Bz1	L-Met-OEt
		.i	ت	ت.
45	ned)	321	128	12
50	(continued)	Boc-L-Glu-0Bz1	Boc-L-Glu-0Bzl	Boc-L-Glu-0Bz]
55	ole 1			
	Table	0-17	. 1-0	D-19

5	(2H), H),	3. 65(3H), 5. 22(2H), H), (6H)	1.36(9H), (1H), 4.03(1H), 6.15(1H), 7.08-7.36(24	. 32(7H), H), H),. H),,
10	00-1.59	43(1H), 3 1), 4.95-9 1), 6.45(1)	1), 1. 36(9 98(1H), 4 1), 6. 15(1 1), 7. 08-7	. 09(3H), ), 1. 30-2. 32 ), 4. 11(2H), ), 5. 14(2H), ), 6. 40(1H), . 55-7. 64(6H)
15	0. 76-0. 96(6H), 1. 00-1. 59(2H) 1. 11(3H), 1. 20(3H), 1. 43(9H),	1. 71-2. 30(5H), 3. 43(1H), 3. 65(3H), 4. 36(1H), 4. 44(1H), 4. 95-5. 22(2H), 5. 44(1H), 6. 28(1H), 6. 45(1H), 7. 08-7. 42(14H), 7. 52-7. 76(6H)	00(3H), 1. 15(3H), 1. 36(9H), 53-2. 26(4H), 3. 98(1H), 4. 03(1H), 12(2H), 5. 33(1H), 6. 15(1H), 56(1H), 6. 89(1H), 7. 08-7. 36(24, 7. 50-7. 58(6H)	76-0.90(6H)), 1.09(3H), 54(3H), 1.22(3H), 1.30-2.32(7H), 39(9H), 3.67(1H), 4.11(2H), 24(1H), 4.50(1H), 5.14(2H), 32(1H), 6.30(1H), 6.40(1H), 14-7.37(14H), 7.55-7.64(6H)
20	0.76-0. 1.11(3H	1. 71-2. 4. 36(1H) 5. 44(1H) 7. 08-7.	1. 00(3H) 1. 53-2. 5 5. 12(2H) 6. 56(1H) H), 7. 50-	0.76-0.90 1.54(3H), 1.39(9H), 4.24(1H), 5.32(1H), 7.14-7.37
	9		9	9
25	(0)			
30	C+8H59N3O8S	m. p. 159, 5- 160, 5	Cs.Hs7NsOeS amorphous	C.s.H. 1 N. O. S. amorphous
35	Trt		<b>⊢</b>	Trt
40	L-11e-0Me		NHCHPh 2	L-Leu-OEt
	-1		Q	Ω
45 F	B21		128	321
-	Boc-L-Glu-OBzl		Boc-L-61u-0Bz1	Boc-L-Glu-OBz1
55 <u>[</u>	D-20		D-21	D-22 [

5 10		02(3H), 1. 12(6H), 1. 40(9H), 60-2. 29(4H), 3. 03(2H), 3. 62(1H), 06(2H), 4. 24(1H), 4. 73(1H), 14(2H), 5. 36(1H), 6. 31(1H), 54(1H), 7. 06-7. 40(19H), 65-764(6H)	11(3H), 1. 19(6H), 1. 22(3H), 39(9H), 1. 52-2. 42(8H), 3. 51(1H), 03(2H), 4. 12(2H), 4. 24(1H), 50(1H), 5. 14(2H), 5. 32(1H), 31(1H), 6. 71(1H), 7. 14-7. 36(14, 7. 56-7. 65(6H)	04(9H), 1. 15(3H), 1. 16(3H), 42(9H), 1. 60-2. 26(4H), 3. 48(1H), 65(3H), 3. 86(1H), 4. 00(1H), 31(1H), 4. 54(1H), 5. 11(2H), 40(1H), 6. 32(1H), 6. 58(1H), 13-7. 36(14H), 7. 59-7. 69(6H)
20		1. 02(3) 1. 60-2. 4. 06(2) 5. 14(2) 6. 54(1) 7. 65-7.	1. 11(3H) 1. 39(9H) 4. 03(2H) 4. 50(1H) 6. 31(1H) H), 7. 56-	0.04(9H), 1.42(9H), 3.65(3H), 4.31(1H), 5.40(1H), 7.13-7.36
25		9	9	9
30		CszHssNsOsS amorphous	CsoHgiN3O10S amorphous	C. B.H. B. 18309SSi amorphous
35		Tr.	Tr.	ال ا
40		L-Phe-OEt	р С-61u-0Et	Si(Me) 3 L-Ser-OMe
45		C		ب ب
50	1 (continued)	Boc L Glu OB: L	Boc-L-Glu-0B21	Boc-L-Glu-0Bzl
55	Table	0-23 8	D-24 B	D-25 B

	. 63-2. 50(8H), 3H), 3. 71-3. 85 1H), 4. 77(1H), . 39(1H), 7. 12- (6H)	. 17(3H), 1. 30 2. 28(4H), 2. 97 2H), 4. 27(2H), . 71(1H), 5. 12 [1H), 6. 31(1H), . 10-7. 42(14	0.94(12H), (9/2H), 1.37 H), 4.04(1H), .12(2H),
	0. 97(6H), 1. 39(9H), 1. 63-2. 50(8H), 3. 44-3. 68(1H), 3. 64(3H), 3. 71-3. 85 (1H), 4. 28(1H), 4. 42(1H), 4. 77(1H), 5. 15(2H), 5. 36(1H), 6. 39(1H), 7. 12- 7. 36(14H), 7. 50-7. 62(6H)	1. 08(3H), 1. 15(3H), 1. 17(3H), 1. 30 (3H), 1. 42(9H), 1. 63-2. 28(4H), 2. 97 (2H), 3. 39(1H), 4. 76(2H), 4. 27(2H), 4. 32(1H), 4. 59(2H), 4. 71(1H), 5. 12 (2H), 5. 46(1H), 6. 23(1H), 6. 31(1H), 6. 81(2H), 7. 03(2H), 7. 10-7. 42(14 H), 7. 54-7. 66(6H)	0.72(3H), 0.80(3H), 0.94(12H), .22-2.40(20H), 1.36(9/2H), 1.37 9/2H), 2.80-3.50(10H), 4.04(1H), .39(1H), 4.50(1H), 5.12(2H), .09-8.07(28H)
	0.97(1H), (1H), 5.15(	1. 08((3H), (2H), 4. 32((2H), (2H), 6. 81((H), 7.	*0.72( 1.22-2 (9/2H) 4.39(1 7.09-8
	<b>.</b>	φ	တ
	C. C.7HssNo0s amorphous	CseHesNoOS amorphous	CeeHsoN.O.,S.
	T t	Trt	N Trt
	L-Pro-OMe	ÇII2COOEt Tyr-OEt	SO3·Bu.N DL-Phe-OH
3)	٥	<b>ـ</b> ــ	٠ .
e 1 (continued	Boc-L-Glu-0Bz1	Boc-L-Glu-0Bz1	Boc-L-Glu-0Bz1
Table	D-26	D-27	D-28

	r				
5		), 1. 41 H), 3. 94 12(2H), 10-7. 32	, 1.83- 4(1H), , 7.10	, 3.73 (8(1H),	(2 (4H), (3 (1H), (1)), (1)
10		1. 09(3H), 1. 19(3H), 1. 27(3H), 1. 41 (9H), 2. 64-2. 93(2H), 3. 48(1H), 3. 94 (2H), 4. 17(2H), 4. 55(1H), 5. 12(2H), 5. 66(1H), 6. 14-6. 33(2H), 7. 10-7. 32 (14H), 7. 52-7. 64(6H)	1. 08(3H), 1. 18(3H), 1. 42(9H), 1. 83- 2. 32(4H), 3. 63-3. 72(1H), 4. 34(1H), 5. 12(2H), 5. 39(1H), 6. 49(1H), 7. 10-7. 43(15H), 7. 48-7. 56(6H)	1. 04(3H), 1. 06(3H), 1. 43(9H), 3. 73 (1H), 4. 00(2H), 5. 69(2H), 6. 68(1H), 7. 10-7. 33(9H), 7. 54-7. 64(6H), 8. 28(1H)	97(6H), 1.37(9H), 1.80-2.62(4H), 18-4.90(3H), 5.69(1H), 6.83(1H), 12-7.30(9H), 7.46-7.61(6H), 06(1H)
15		1. 19 (3H) -2. 93 (2H) (2H), 4. E 5. 14-6. 3 2-7. 64 (6	1. 18(3H), 3. 63-3. 72 5. 39(1H), ), 7. 48-7.	1.06(3H (2H), 5. (9H), 7.	1.37(9H (3H), 5. (9H), 7.
20		1.09(3H), 1.19(3H), 1.27(3H (9H), 2.64-2.93(2H), 3.48(1 (2H), 4.17(2H), 4.55(1H), 5. 5.66(1H), 6.14-6.33(2H), 7. (14H), 7.52-7.64(6H)	1.08(3H), 2.32(4H), 5.12(2H), -7.43(15H)	1.04(3H), (1H), 4.00 7.10-7.33 8.28(1H)	0.97(6H), 4.18-4.90 7.12-7.30 8.06(1H)
25		9	3	7	7
30		C++Hs:N3OsS amorphous	C.1H.8N2O7S amorphous	CaiHasN2OsS amorphous	C3+H+oN2O7S amorphous
35		Trt	Trt	<u>+</u>	T
40		Gly-OEt	но	Gly-OH	НО
	1)	ب ۔	ب	Q	۵
45	inue	)Bz1	)B21		110
50	e 1 (continued	Boc-L-Asp-0Bz	Boc-L-Glu-0Bz	Вос	Boc-L-Glu-Off
55	Table	D-29	D-30		E - 2

				T	
5		. 53 1H), . 49-	H), H), 54-	4), 1.71 4, 20- 06- 05-	1), 1.76
10		, 1.82-2. 1), 5.68(1), 2.(9H), 7.	6.51(1 8(9H),70	, 1. 45(9) 70(2H), 0(2H), 7. 4(6H), 8.	, 1. 39(91 34(4H), ( H)
15		0. 96(6H), 1. 36(9H), 1. 82-2. 53 (4H), 4. 20-4. 85(3H), 5. 68(1H), 6. 81(1H), 7. 13-7. 32(9H), 7. 49- 7. 63(6H), 8. 09(1H)	1. 08(3Ḥ), 1. 11(3ℍ), 1. 97(3ℍ), 3. 89(1ℍ), 3. 97(2ℍ), 6. 51(1ℍ), 6. 62(1ℍ), 7. 12-7. 38(9ℍ), 7. 54- 7. 67(6ℍ), 7. 00-8. 00(1ℍ)	0.89(3H), 0.97(3H), 1.45(9H), 1.71 -2.80(4H), 3.47-3.70(2H), 4.20- 4.73(2H), 5.07-5.50(2H), 7.06- 7.27(9H), 7.47-7.64(6H), 8.05- 9.00(3H)	1. 05(3H), 1. 06(3H), 1. 39(9H), 1. 76 -2. 56(4H), 3. 66-4. 34(4H), 6. 64 (1H), 6. 00-8. 16(19H)
20		0.96(6H (4H), 4. 6.81(1H 7.63(6H	1. 08(3H) 3. 89(1H) 6. 62(1H) 7. 67(6H)	0.89(3H) -2.80(4I 4.73(2H) 7.27(9H) 9.00(3H)	1.05(3H) -2.56(4F)
25			7	7	7
30		Co.H.oN2O7S amorphous	C28H30N2O+S amorphous	CseH+3N3OeS amorphous	C38H+3N3O8S amorphous
35		Trt	T T	F -	Trt
40		НО	G1y-0H	G1y-0H	G 1 y - OH
45		Δ			Q
50	1 (continued	Boc-D-Glu-OH	N C	Boc-L-Glu-011	Boc-L-Glu-()
55	Table	ന   ഡ	4	ო გ	(T) (Q)

55	50	45	40	35	30	25	20	15	10	5
Table	e l (continued)	1ed)								
E-7	Boc-D-G1u-0H	Ω	G1y-0H	Trt	C38H+3N3O8S	7	0.89(3H), 1.70-2.76	89(3H), 0.96(3H), 1.45(9H), 70-2.76(4H), 3.44-3.80(2H)	1.45(9H), -3.80(2H),	
							4. 20-4. 70(211), 5.	(211), 5. 10-5.	-5.52(2H),	
					•		7.02-7.36	.02-7.36(9H), 7.44-7.	-7.68(6H),	
		<del></del>		•			7.90-9.45(3H)	(3H)		
							*0.77(3H)	*0.77(3H), 0.81(3H), 1.38(9H)	1.38(9H),	
E-8	Boc-L-61u-	<u>۔</u>	G1y-0H	Trt	C38H+3N3O8S	7	1.65-2.10	1.65-2.10(2H), 2.15-2.40(2H),	-2.40(2H),	
					amorphous		3.34(1H),	3.34(1H), 3.58-3.89(2H), 4.07	(2H), 4.07	
							(1H), 4.40	(1H), 6.80	(1H), 4. 40(1H), 6. 80-7. 88(16H)	
							7.77(1H),	7.77(1H), 8.42(1H), 12.28(1H)	12.28(1H)	
							0.98(3H),	98(3H), 1.06(3H), 1.34(9H),	1.34(9H),	
요 - 3	Boc-L-18p-011	0	Gly-011	Trt	C3 5 H + 1 N3 O 8 S	7	2.64-3.08	(2H), 3.60	2. 64-3. 08(2H), 3. 60-4. 70(4H),	
					amorphous		5.90(1H),	6.90 - 7.30	90(1H), 6.90-7.30(11H), 7.44	
							-7.66(6H)	66(6H), 9.54(2H)		
							*0.78(3H)	*0.78(3H), 0.82(3H), 1.26(3H),	, 1. 26(3H),	
E-10	Boc-L-61u-011		L-Ala-OH	Trt	C37H+5N3O8S	7	1.39(9H),	.39(9H), 1.60-2.54(4H), 3.	(4H), 3.33	
		<del></del>			amorphous	-	(IH), 3.93	(1H), 3. 93(1H), 4. 15(1H), 4. 53	(IH), 4.53	
						<del></del>	(1H), 7.04	-7.38(10H	(1H), 7.04-7.38(10H), 7.49-7.59	<u> </u>
							(6H), 8.11	(6H), 8.11(1H), 8.38(1H), 12.	(1H), 12.20	
			-				(11)			
				ļ		,				

55	50	45	40	35	30	25	15	10	5
Table	e 1 (continued)	d)			•				
-		-	:	Ę	1		0.86(3H), 0.89(3H), 1.02(3H)	H), 1. 02(3H),	
<u>.</u>			L-Val-OH	 	C39H49N3O8S		1.06(3H), 1.41(9H), 1.80-2.55	III), 1.80-2.55	
					amorphous		(5II), 4. 06(1H), 4. 24-4. 48(2H),	. 24-4. 48(211),	
		· <del></del>					5. 68(111), 7. 07-7. 33(1011), 7. 43	. 33(1011), 7. 43	
							(1H), 7. 53-7. 65(6H), 8. 50(2H)	(6H), 8.50(2H)	
	•						0.87(3H), 0.90(3H), 1.04(3H), 1	11), 1.04(311), 1.08	82
E-12	Boc-L-G1u-011		L-Val-OH	Trt	C39H49N3O8S	7	(3H), 1. 41(9H), 1. 81-2. 57(5H),	.81-2.57(5H),	
		۰,			amorphous		4.07(1H), 4.25-4	4.07(1H), 4.25-4.50(2H), 5.69(1H),	
							7.03-7.30(10H), 7.40(1H), 7.51	7.40(111),7.51-	
							7. 66(6H), 8. 52(2H)	(11)	
							*0.77-0.90(6H), 0.87(3H), 0.90	0.87(3H), 0.90	
E-13	Boc-L-Glu-01	<i>ം</i>	L-Leu-OH	Trt	C40H51N3O8S	_	(3H), 1. 39(9H), 1. 30-2. 12(5H),	.30-2.12(5H),	
					amorphous		2.36(2H), 3.68(1	2.36(2H), 3.68(1H), 3.94(1H), 4.22	2
							(1H), 4. 49(1H), 7. 08-7. 35(10H)	.08-7.35(10H),	
							7.50-7.62(6H),8	7.50-7.62(6H), 8.07(1H), 8.18(1H)	
							12.32(1H)		
							*0.96(3H), 1.12(3H), 1.37(9H),	3H), 1. 37(9H),	
E-14	Boc-L-Glu-OH	<u>`</u>	L-Pro-OH	Trt	C39H47N3O8S	2	1. 57-2. 52(8H), 3. 06-3. 62(3H),	.06-3.62(3H),	
				<del></del>	amorphous		3.93(1H), 4.14(1	3.93(1H), 4.14(1H), 4.27(1H), 7.09	တ
							(1H), 7. 10-7. 38(9H), 7. 44-7. 62	9H), 7.44-7.62	
							(6H), 8, 10(1H), 12, 40(1H)	2. 40(1H)	

55	50	45	<b>4</b> 0	35	30	25	20	15	10	5
Table	l (continued)	_								
- 3 S 1 - 5	Boc-L-Glu-()]		L-Phe-Oil	T	C.3H.sN3OsS amorphous	7	*0.72(3H), 0.79(3H), 1.39(9H), 1.66-2.12(2H), 2.20-2.36(2H), 2.79-3.12(2H), 3.84-4.05(1H),	0.79(3H), 2H), 2.20- 2H), 3.84-	1.39(9H), 2.36(2H), 4.05(1H),	
							4. 42(1H), 4. 47(1H), 7. 06-7. 34 (15H), 7. 48-7. 60(6H), 7. 97(1H) 8. 32(1H), 12. 50(2H)	42(1H), 4. 47(1H), 7 5H), 7. 48-7. 60(6H) 32(1H), 12. 50(2H)	. 06-7.34 , 7.97(1H),	
E-16	Boc-L-Glu-011		L-Tyr-OH	Trt	C43H+8N3O8S amorphous.	7	1. 00(6H), 1. 43(9H), 1. 2. 77-3. 17(2H), 3. 84(14, 70(1H), 5. 74(1H), 6. 94(2H), 6. 94(2H), 6. 94(2H), 6. 94(2H), 6. 94(2H), 6. 94(2H), 9. 94(	. 43(9H), 1 (2H), 3.84 (3.74(1H), (1H), (1H), 6.94	1. 00(6H), 1. 43(9H), 1. 80-2. 50(4H), 2. 77-3. 17(2H), 3. 84(1H), 4. 26(1H), 4. 70(1H), 5. 74(1H), 6. 57(1H), 6. 71 (2H), 6. 83(1H), 6. 94(2H), 7. 09-7. 38	71 71 7. 38
	L						(9H), 7, 53- 0, 99(3H), 1	7.63(6H),	(9H), 7, 53-7, 63(6H), 6, 50-9, 90(3H) 0, 99(3H), 1, 09(3H), 1, 43(9H), 1, 85-	85-
E-17	Boc-L-Glu-OH	<u>ا</u>	L-G1u-OH	₩ ₩	CasH47N3O10S amorphous	_	2. 64(8H), 3 (1H), 5. 81( (10H), 7. 53	3. 91(1H), (1H), 6. 98 2-7. 74(6H	2. 64(8H), 3. 91(1H), 4. 23(1H), 4. 49 (1H), 5. 81(1H), 6. 98(1H), 7. 10-7. 43 (10H), 7. 52-7. 74(6H), 8. 20-11. 6	. 49 7. 43 6
-18 8	Boc-L-Glu-OH		NHCHPh2	Trt	C47H51N3O8S amorphous		(3H) 1. 06(6H), 1. 40(9H), 1. 70-2. 50 4. 12(1H), 4. 26(1H), 5. 48(1H), (1H), 6. 61(1H), 6. 94-7. 34(20H) 7. 46-7. 55(6H), 6. 90-8. 00(1H)	1.40(9H), 4.26(1H), (1H), 6.94 (6H), 6.90	(3H) 1. 06(6H), 1. 40(9H), 1. 70-2. 50(4H), 4. 12(1H), 4. 26(1H), 5. 48(1H), 6. 06 (1H), 6. 61(1H), 6. 94-7. 34(20H), 7. 46-7. 55(6H), 6. 90-8. 00(1H)	4H),

••	50 55	45	40	35	30	25	20	15	10	5
Table	1 (continued	ued)								
E-19	Boc-L-GJu-UII		L-Asp-OH	Trt	C38 H+5 N3010S	7	*0.79(3H 1.60-2.7	*0.79(3H), 0.82(3H), 1.39(9H), 1.60-2.78(6H), 3.36(1H), 3.95(1H),	), 1. 39(9H 5(1H), 3. 9	4), 35(1H),
					amorphous		4. 40-4. 58 7. 49-7. 60 12. 51(2H)	.40-4.58(2H),7.08-7.38(10H), .49-7.60(6H),8.11(1H),8.37(1H), 2.51(2H)	8-7.38(10 1(1H), 8.3	37(1H),
E-20	Boc-L-G14-0		L-Met-OH	T + +	CasHtsNaOsSz amorphous	7	*0.78(3H) -2.60(8H) (1H), 4.2	*0.78(3H), 0.82(3H), 1.38(9H), 1. -2.60(8H), 2.00(3H), 3.33(1H), 3. (1H), 4.28(1H), 4.50(1H), 7.10-7.	), 1. 38(91) ), 3. 33(11) 0(111), 7. 1	1), 1. 64 1), 3. 95 10-7. 36
							8.30(1H)	8.30(1H), 12.52(1H)	7, 0. 10(1	· ( )
E-21	Boc-L-Glu-011		L-11e-0H	F-	C40Hs1N3O8S amorphous	7	*0.70-0. 1.38(9H) (2H), 3.3 4.54(1H) 7.60(6H),	*0.70-0.90(12H), 1.02-1.54(2H), 1.38(9H), 1.66-2.10(3H), 2.22-2.42(2H), 3.32(1H), 3.93(1H), 4.11(1H), 4.54(1H), 7.11-7.37(10H), 7.48- 7.60(6H), 8.00(1H), 8.08(1H), 12.42	02-1.54( 0(3H), 2.2 3(1H), 4.1 7(10H), 7.	. 54(2H), , 2. 22-2. 42, , 4. 11(1H), ), 7. 48- (1H), 12. 42
							(1H)			

55		50	<b>45</b> .	40	35	30	25	20	15	10	5
Table		(continued)	_					;			
E-22	Boc-L-Glu-011	110-n1	Q	NIICIIPh 2	F-	C <sub>17</sub> H <sub>51</sub> N <sub>3</sub> O <sub>8</sub> S m.p.125.5-		1. 05(3H), 1. 67-2. 38 5. 46(1H), 7. 00-7. 30	1. 05(3H), 1. 15(3H), 1. 38(9H) 1. 67-2. 38(4H), 3. 90(1H), 4. 0 5. 46(1H), 6. 13(1H), 6. 84(1H) 7. 00-7. 30(21H), 7. 46-7. 58(6	1. 05(3H), 1. 15(3H), 1. 38(9H), 1. 67-2. 38(4H), 3. 90(1H), 4. 01(1H), 5. 46(1H), 6. 13(1H), 6. 84(1H), 7. 00-7. 30(21H), 7. 46-7. 58(6H)	(1H),
E-23	Boc-L-G	110-n15-7	Ω .	L-Leu-OH	. <del>(-</del>	CtoHsiNoOgS amorphous	7	*0.63-0.9 1.38(9H), 3.88(1H), 7.04(1H), (6H), 8.14 (1H)	63-0.92(12H), 1.25 8(9H), 2.14-2.56(2 8(1H), 4.22(1H), 4. 4(1H), 7.15-7.36(9 ), 8.14(1H), 8.42(1	*0.63-0.92(12H), 1.25-2.03(5H), 1.38(9H), 2.14-2.56(2H), 3.34(1H), 3.88(1H), 4.22(1H), 4.54(1H), 7.04(1H), 7.15-7.36(9H), 7.47-7.59 (6H), 8.14(1H), 8.42(1H), 12.44 (1H)	1), (1H), -7.59
E - 24	Boc-L Glu-011	II 0 - n 1	Ω	L-Phe-OH	7	C.3H.sN3OsS amorphous		*0.59(6H), 2.20-2.5 3.37(1H), 7.06-7.37 8.02(1H),	39(9H), 2. 3, 94(1H), 7. (15H), 7. 8, 37(1H),	*0.59(6H), 1.39(9H), 1.78-2.10(2H), 2.20-2.55(2H), 2.79-3.11(2H), 3.37(1H), 3.94(1H), 4.31-4.51(2H), 7.06-7.37(15H), 7.43-7.56(6H), 8.02(1H), 8.37(1H), 12.60(1H)	), (2H), ),

50	45	40	35	30		15 20	10	5
Table 1 (continued)	ed)							
E-25 Boc-L-Glu-OII	0	L-G1u-011	Trt	CasH+7N3O10S amorphous		*0.74(3H), 0.80(3H), 1.39(9H), 1.62-2.08(4H), 2.12-2.54(4H), 3.35(1H), 3.88(1H), 4.24(1H), 4.53 (1H), 7.04(1H), 7.11-7.37(9H), 7.47-7.60(6H), 8.02(1H), 8.46(1H), 12.34(2H)	0(3H), 1. 39 2. 12-2. 54 (1H), 4. 24 7. 11-7. 37 8. 02(1H),	(9H), (4H), 1H), 4.53 (9H), 8.46(1H),
E-26 Boc-L-Glu-Oil	د.	L-Ser-OH	۲ ۲	C37H45N3O9S amorphous		*0.80(3H), 0.85(3H), 1.39(9H), 1.62-2.12(2H), 2.22-2.53(2H), 3.34(2H), 3.56-3.77(2H), 3.93(1H), 4.24(1H), 4.54(1H), 7.06-7.35(10H), 7.48-7.61(6H), 8.10(1H), 8.19(1H), 12.44(1H)	5(3II), 1. 39 , 2. 22-2. 53 -3. 77(2H), (1H), 4. 54( ), 7. 48-7. 6 (1H), 12. 44	(9H), (2H), 1H), 1(6H), (1H)
E-27 Boc-L-Glu-OII	Q	L-Pro-OH	Tr	C39H+7N3O8S amorphous	-	*0.85(3H), 0.88(3H), 1.38(9H), 1.65-2.46(8H), 3.33(1H), 3.30-3.70 (2H), 3.75-3.97(1H), 4.20(1H), 4.80(1H), 6.99(1H), 7.14-7.17(9H), 7.43-7.55(6H), 8.17(1H), 12.42(1H)	3(3H), 1.38 3.33(1H), 7(1H), 4.20 (1H), 7.14- 8.17(1H),	(9H), 3.30-3.70 (1H), 7.17(9H), 12.42(1H)

<b>45</b> <b>50</b>	45	40	35	30	25	20	15	10
(continued)								
Boc-L-Glu ()[[		ÇII2 COOH Tyr-OII	٦ . ب	C+5H51N3O11S amorphous	<i>-</i>	*0.75(3H), 0.81(3H), 1.39(9H), 1.60-2.14(2H), 2.21-2.46(2H), 2.75-3.02(2H), 3.35(1H), 3.98( 4.37(1H), 4.48(1H), 4.60(2H), 6(2H), 7.04-7.38(12H), 7.50-7.6 (6H), 8.03(1H), 8.27(1H), 12.67	). 81(3H), !H), 2. 21- !H), 3. 35( 48(1H), 4 7. 38(12H) !H), 8. 27(	*0.75(3H), 0.81(3H), 1.39(9H), 1.60-2.14(2H), 2.21-2.46(2H), 2.75-3.02(2H), 3.35(1H), 3.98(1H), 4.37(1H), 4.48(1H), 4.60(2H), 6.75 (2H), 7.04-7.38(12H), 7.50-7.62 (6H), 8.03(1H), 8.27(1H), 12.67(2H)
Boc - L - G I u - O II		SO <sub>3</sub> ·Bu <sub>4</sub> N DL-Phe-OH	N Trt	CssHs+N+O11Sz amorphous	7	*0.76(3H), 0.82(3H), 0.94(12H), 1.20-1.42(8H), 1.38(9H), 1.47-1 (8H), 1.72-2.15(2H), 2.20-2.41( ,2.80-3.30(11H), 3.94(1H), 4.41 (1H), 4.49(1H), 7.07-7.38(11H), 7.43-7.66(9H), 8.04(1H), 8.28(1 12.45(1H),	3. 82(3H), 3H), 1. 38( 2. 15(2H), (11H), 3. 9 1H), 7. 07- 3H), 8. 04(	*0,76(3H),0.82(3H),0.94(12H), 1,20-1,42(8H),1.38(9H),1.47-1.68 (8H),1.72-2.15(2H),2.20-2.41(2H), 2.80-3.30(11H),3.94(1H),4.41 (1H),4.49(1H),7.07-7.38(11H), 7.43-7.66(9H),8.04(1H),8.28(1H), 12.45(1H),
Boc-L-Asp-OH	L	Gly-0H	↑r t	CasH41N3OsS amorphous	<u>-</u>	1. 12(3H), 1. 15(3H), 1. 28(9H), 2. 62-3. 05(2H), 3. 72-4. 32(3H), 4. 51(1H), 5. 93(1H), 6. 38-7. 39 (11H), 7. 53-7. 64(6H), 9. 63(2H)	15(3H), 1 2H), 3. 72- 93(1H), 6 -7. 64(6H)	. 28(9H), 4. 32(3H), . 38-7. 39

						- i				r		Ţ	~~		_		_	
5		E),	,	47-7.5				53-7.61		?H),		2.22	1), 4. 48		2.22	<u>`</u>		
10		*0.85(3H), 0.89(3H), 1.38(9H), 1.62-2.11(2H), 2.23-2.38(2H),	3. 40(IH), 3. 91(1H), 4. 11(1H),	7.03(1H), 7.14-7.36(9H), 7.47-7.57	. 52(1H)	1.04(3H), 1.06(3H), 1.43(9H)	74(1H), 4.00(2H), 5.63(1H)	65(1H), 7. 10-7. 35(9H), 7. 53-7.		**1. 42(3H), 1. 49(3H), 3. 98(2H),	V.	1	(2H), 2. 45-2. 59(2H), 3. 93(1H), 4. 43		**1.37(3H), 1.42(3H), 2.08-2	(2H), 2. 49-2. 60(2H), 3. 97(1H),		
15		H), 0.89(3	), 3. 91(1H	), 7. 14-7.	(6H), 8. 03(1H), 12. 52(1H)	), 1.06(3H	), 4.00(2H	), 7. 10-7.	33(1H)	3H), 1. 49(		**1. 38(3H), 1. 43(3H), 2. 01	15-2.59(2		(H), 1. 42(	9-2.60(2)		
20		*0.85(3)	3.40(IH)	7.03(1H)	(6H), 8.	1.04(3H)	3.74(1H)	6.65(1H)	(6H), 8. 63(1H)	**1.42(	3.99(1H)	**1.38(3	(2H), 2. 4	(1H)	**1.37(3	(2H), 2. 4	4. 41(1H)	
0.5		7				7				— ∞		<del>                                     </del>	∞			∞		-
25						2			-	20	· · ·		ICQ			CQ	·	
30	i	. C3+H+0N2O7S	amorphous			C31H36N2O5S2	amorphous			C7H1+N2O3S·HCQ	49-54C decomp.		C, OH, BN2O5S·HCQ	84-89° decomp.		C.oH.BN2O5S.HCQ	89-93T decomp.	
35		Trt				Trt				H			=			==		
40		НО	,	-		Gly-0H				G1y-0H			HO			НО		
<b>4</b> 5	d)									<u>a</u>			<u>a</u>			Q		
50 55	e 1 (continued	Boc-L-G1u-011		,		Вос				==		<u> </u>	II-L-GIu-0II			II-D-G I n-0 II		
55	Table	E-31				E-32				-			F-2			F-3		

	ſ			Т						1				T						
5		3H),		2.21	H), 3.97		2.23	н),			-2.21	Н),			.2.27	H), 4.18		.3.17	39(1H)	
10 ,		), 2.01(		), 2.06-	, 3.93(2		), 2.03-	, 3.94(3			1), 2.07-	, 3, 93(2			(), 2.04-	, 3, 94(2		(), 2.89-	(1H), 4.	
15		1.42(3H	37(1H)	1.41(3H	2.69(2H)	(H)	1.42(3H	2. 60(2H)			I. 41 (3H	2. 67 (2H)	38(1H)		1. 42(3H	2.54(2H)	(H)	1.40(3H	2H), 4.26	
20		**1. 35(3H), 1. 42(3H), 2. 01(3H)	3. 94(2H), 4. 37(1H)	**1. 35(3H), 1. 41(3H), 2. 06-2.	(2H), 2. 41-2. 69(2H), 3. 93(2H), 3.	(1H), 4. 38(1H)	**1.37(3H), 1.42(3H), 2.03-	(2H), 2, 43-2, 60(2H), 3, 94(3H)	4.41(1H)	,	**I. 35(3H), I. 41(3H), 2.07	(2H), 2. 41-2. 67(2H), 3. 93(2H)	3.96(1H), 4.38(1H)		**1.37(3H), 1.42(3H), 2.04-2.27	(2H), 2. 40-2. 54(2H), 3. 94(2H), 4.	(1H), 4. 47(1H)	**1. 35(3H), 1. 40(3H), 2. 89-3. 17	(2H), 3. 92(2H), 4. 26(1H), 4. 39(1H)	
	,				~			∞				∞				∞			∞	
25			•	-		ď.	-	8		•		8					ရွှဲ			ď
30		CoHIBN2O+S	65-72° decomp.		C. 2 H 2 , N 3 O 8 S • H C Ø	121-125C decomp		C.2H21N3O8S-HCQ	113-1170	decomb.		C, 2H2, N3OBS·HCQ	127-131°C	decomb.		C12H21N3O8S.HCQ	129-135Cdecomp		C11H19N3O8S-HCQ	130-134 Cdecomp.
35		×			Ħ			H				Ħ				Ħ			Ħ	
40		Gly-0H			Gly-0H			Gly-0H				Gly-0H				Gly-0H			Gly-0H	
45	(F							۵								ب			Ω	
50	e 1 (continued	Λc			II-L-G u-011			H-L-G 1 u-011				H-D-G1u-011				H-L-Glu-		<u></u>	H-L-Asp-011	
55	Table	j. – G			F-5			F - 6				T-				F-8			g - 4	

	55	50	45	40	35	25 30	20	15	10	5
Table		(continued		•						
F - 1 0	H-L-Glu-01	110-		L-Ala-OH	=	C <sub>13</sub> H <sub>2</sub> +N <sub>3</sub> O <sub>6</sub> S·HCQ 8 125-128°C decomp.		**1.35(6H), 1.40(3H), 2.0 (2H), 2.40-2.66(2H), 3.97 (1H), 4.37(1H)	), 2. 06-2. 21 , 3. 97(1H), 4.	21, 4. 28
- C		110-	_ <u>`</u>	, L-Val-OH	Ж	C.sH2,N3O6S.HCQ 8 128-133C decomp.		**0.87(3H), 0.90(3H), 1.36(3H), 1.40 (3H), 1.98-2.30(3H), 2.38-2.70(2H), 3.98(1H), 4.13-4.23(1H), 4.46(1H)	), 1.36(3H), 2.38-2.7 (1H), 4.46	), 1.40 0(2H), (1H)
F-12	H-L-Glu-OH	Н0-	۵	L-Val-OH	Н	C15H27N3O6S-HCQ 8 119-124T decomp.	**0.89(3H), (3H), 1.96-2 3.95(1H), 4.	**0.89(3H), 0.92(3H), 1.34(3H), 1. (3H), 1. (3H), 1.96-2.31(3H), 2.42-2.61(2H), 3.95(1H), 4.07-4.20(1H), 4.92(1H)	), 1. 34(3H) , 2. 42-2. 61 (1H), 4. 92(	3H), 1.39 .61(2H), 92(1H)
F-13	H0-n15-7-H	НО-	<del>ان</del>	L-Leu-OH	Н	C <sub>18</sub> H <sub>29</sub> N <sub>3</sub> O <sub>6</sub> S·HC2 8 114-119°C decomp.	**0.78(3H), 0. 1.40(3H), 1.53 (2H), 2.46-2.5 (1H), 4.38(1H)	**0.78(3H), 0.84(3H), 1.35(3H), 1.40(3H), 1.53-1.72(3H), 2.03-2.17 (2H), 2.46-2.58(2H), 3.92(1H), 4.34 (1H), 4.38(1H)	), 1. 35(3H (3H), 2. 03 , 3. 92(1H)	3H), 03-2.17 H), 4.34
F - 1 4	H-L-Glu-OH	. НО-		L-Pro-OH	Œ	C <sub>15</sub> H <sub>25</sub> N <sub>3</sub> O <sub>6</sub> S·HC@8 148-152° decomp.	**1.39(3H), 1. (8H), 3.80(2H) 4.60-4.80(1H)	39(3H), 1. 41(3H), 1. 86-2., 3. 80(2H), 3. 97(1H), 4. 35-4. 80(1H)	), 1.86-2. (1H), 4.35	2.67 35(1H)

	55	50	45	40	35	30		10	
lable	<del>-</del> 1	(continued)							
							<u> </u>	**1. 24(3H), 1. 26(3H), 1. 96-2. 24	
F-15	H0-110-7-K	H0-	ب	L-Phe-OH	Ħ	C19H27N3O8S+HCQ	∞	(2H), 2. 28-2. 58(2H), 2. 82-3. 29(2H),	2H),
: :					_	119-125°C		3.97(1H), 4.30(1H), 4.69(1H),	-
	•					decomb.		7.13-7.32(5H)	
							-	**1. 24(3H), 1. 26(3H), 1. 98-2. 24	
F-16	H-L-G1u-OH	, HO-	د	L-Tyr-OH	=	C19H27N3O7S.HCQ	∞	(2H), 2. 29-2. 61(2H), 2. 74-3. 26(2H),	2H),
						133-1390		3.94(1H), 4.30(1H), 4.69(1H), 6.72	7.2
			-			decomp.		(2H), 7.05(2H)	
							*	**1. 38(3H), 1. 42(3H), 1. 83-2. 30(4H)	
F-17	-    -    -    -	110-		L-G1u-OH	=	C, sH25N3O+S.HCQ	∞	2. 39-2. 65(4H), 3. 95(1H), 4. 40(1H),	H),
						140-150°C		4.42(1H)	
						decomb.			
								*1. 29(3H), 1. 33(3H), 1. 85-2. 67(2H),	2H),
7 - 1 ⊗	H-[,-G]u-0H	110-		NHCHPh <sub>2</sub>	Ħ	C23H29N3O+S-HCQ	∞	3.40(1H), 3.86(1H), 4.70(1H), 6.12	1.2
						140-147C		(1H), 7. 12-7. 43(10H), 8. 20(1H),	
						десошр.		8.50(1H), 9.13(1H)	
								**1.39(3H), 1.44(3H), 2.10-2.23	
F-19	-L-Glu-0	110-	ب	L-Asp-OH	H	C1+H22N3O8S-HC2	∞	(2H), 2. 51-2. 62(2H), 2. 94(2H), 3. 97	. 97
						128-133C		(1H), 4. 41(1H)	
						decomb.			

55	<b>45</b> 50	45	40	35	25 30	15	5
Table	1 (continued						
F-20	II-1,-G1u-0II		L-Met-OH	×	C.sHz8N3O8S2. 8 HC2 115-119°Cdecomp.	 **1.39(3H), 1.44(3H), 1.93-2.28 (4H), 2.04(3H), 2.41-2.70(4H), 4.00 (1H), 4.40(1H), 4.54(1H)	33-2.28 (4H), 4.00
F-21	H-L-Glu-OH	د.	L-11e-0H	m:	CieH29N3OeS.HC@ 8 121-126U decomp.	**0.83(3H), 0.89(3H), 1.05-1.56 (2H), 1.38(3H), 1.42(3H), 1.76-1.96 (1H), 2.06-2.30(2H), 2.43-2.72(2H), 4.01(1H), 4.25(1H), 4.47(1H)	1.76-1.96 1.76-1.96 3-2.72(2H),
F - 22	H-L-Glu-OH	۵	NHCHPh 2	H	C23H29N3O4S.HC@ 8 120-125t decomp.	 *1.30(3H), 1.35(3H), 1.96-2.15 (2H), 2.36-2.57(2H), 2.80(1H), 3.55 (2H), 3.85(1H), 4.72(1H), 6.14(1H), 7.12-7.48(10H), 8.19(1H), 8.49(2H), 9.12(1H)	5-2.15 1(1H), 3.55 6.14(1H), , 8.49(2H),
F-23 H	II-L-G1u-011	Ω	L-Leu-OH	æ	C.eHzsNsOeS.HC@8 125-129°C decomp.	 **0.70-0.79(6H), 1.36(3H), 1.41 (3H), 1.50-1.82(3H), 2.06-2.31(2H), 2.42-2.68(2H), 4.01(1H), 4.33(1H), 4.43(1H)	(), 1. 41 i-2. 31(2H), 4. 33(1H),

50	(cont	II-L-G1u-0II	7 11-L-Glu-01	H-L-Glu-OH	H-L-Glu-OH
45	(continued)				П
		D - D	D-77	\ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \	
40		L-Phe-011	L-Glu-0H	L-Ser-OH	L-Pro-OH
35		Ħ	æ	H	H
25 30		C. 9 H 2 7 N 3 O 6 S · HCQ 126-129°C decomp.	C.sH25N3O4S.HCQ 120-123C decomp.	C13H23N3O7S-HCQ 8	C <sub>15</sub> H <sub>25</sub> N <sub>3</sub> O <sub>8</sub> S·HC@ 8 137-142° decomp.
		∞	∞	∞	∞
15 20		*1. 13(3H), 1. 18(3H), 2. 41-2. 66(2H), 2. 53(H), (2H), 3. 60(1H), 3. 86(H), 4. 51(1H), 7. 11-7, 40(H), 8. 20-8. 80(3H), 12. 50(H)	*1.33(3H), 1.37(3H), 1.65-2.13(4H) 2.26-2.39(2H), 2.40-2.57(2H), 2.79 (1H), 3.46(3H), 3.88(1H), 4.23(1H), 4.61(1H), 8.14(1H), 8.41(2H), 8.48 (1H), 12.10(1H)	*1. 40(6H), 1. 88-2. 20(2H), 2. 26-2. 6 (2H), 2. 79(1H), 3. 40(2H), 3. 58(3H), 3. 86(1H), 4. 25(1H), 4. 65(1H), 8. 11 (1H), 8. 20-8. 44(3H), 12. 65(1H)	*1. 33(3H), 1. 38(3H), 1. 76-2. 24(6H), 2. 30-2. 60(2H), 2. 93(1H), 3. 50(2H), 3. 60-3. 95(3H), 4. 21-4. 30(1H), 4. 92 (1H), 8. 22-8. 62(3H), 12. 50(1H)
10			(3H), 1 2. 40-2. 3. 88(1H 1H), 8. 4	-2. 20(2H) 3. 40(2H) 1H), 4. 65 (3H), 12.	H), 1. 38(3H), 1. 76-2. 24(6 60(2H), 2. 93(1H), 3. 50(2H 95(3H), 4. 21-4. 30(1H), 4. 22-8. 62(3H), 12. 50(1H)
5		10-2.13(2H), 1, 2.41-2.58 1, 3.45(1H), 1, 8.12(1H), 1)	3H), 1. 37(3H), 1. 65-2. 13(4H), 3. 39(2H), 2. 40-2. 57(2H), 2. 79. 46(3H), 3. 88(1H), 4. 23(1H), H), 8. 14(1H), 8. 41(2H), 8. 48. 2. 10(1H)	), 2. 26-2. 64 , 3. 58(3H), (1H), 8. 11 65(1H)	6-2.24(6H), ,3.50(2H), 0(1H),4.92 50(1H)

55	50	45	40	35	30		15	5
Table	1 (continued	d)						
F - 28		<u> </u>	- CH2COOH	H	C2.1H29N3O9S.HCQ 120-124T decomp.	∞	**1. 26(6H), 2. 01-2. 19(2H), 2. 2. 62(2H), 2. 80-2. 96(1H), 3. 12(1H), 3. 97(1H), 4. 32(1H), 4. 66 6. 85(2H), 7. 15(2H)	2.34- 12-3.25 66(3II),
F-29	Н-L-Glu-ОН		SO3H DL-Phe-OH	æ	C19H27N3O9S2. HC2 216-220°C decomp.	∞	*1. 32(6H), 1. 86-2. 03(2H), 2. 24-2. 44 (2H), 2. 63(1H), 3. 05-3. 22(2H), 3. 78 (4H), 3. 96(1H), 4. 46-4. 61(2H), 7. 15 -7. 28(2H), 7. 42-7. 61(2H), 7. 86(1H), 8. 26-8. 58(3H)	24-2.40 ), 3.78 ), 7.15 86(1H),
F-30	H-L-Asp-OH	ے	G1y-0H	m .	C.3H.sN3OsS.HC@ 146-149C decomp.	∞	**1.39(3H), 1.45(3H), 2.94-3.21 (2H), 3.98(2H), 4.26(1H), 4.45(1H)	. 21 5(1H)
F-31	II-L-Glu-OII		НО	Ħ	C.o.H.sN2OsS.HCQ 52- 55° decomp.	∞	**1.38(3H), 1.44(3H), 2.10-2.24 (2H), 2.53-2.62(2H), 4.01(1H), 4.43 (1H)	. 24

		ν.

**1.46(3H), 1.54(3H), 4	as respective
∞	
H <sub>1+</sub> N <sub>2</sub> O <sub>3</sub> S·HCQ .5-59° decomp.	re isolated
C, 57	3
ж	32
Gly-0H	F-1 to F-3 and F-32 were
_3	+ C
	; <u>[*</u>
Н	Compounds
F-32	
	-32 II L G1y-OH H C <sub>7</sub> H <sub>1+</sub>

Table 1 (continued)

s 8 to F-3 and F-32 were isolated Compounds F-1 hydrochlorides.

measured in DMSO-d<sub>6</sub>

 $\ast\ast,$  measured in  $\text{D}_2\text{O}$ 

Working Example 1 (Synthesis of the Compound 8)

To the solution of (N-γ-L-glutamyl-D-penicillamyl)glycine hydrochloride (F-5) (0.3 g) in 1N-hydrochloric acid (0.81 ml) and methanol (1.6 ml), was added dropwise at room temperature the solution of sodium nitrite (0.11 g) in water (0.5 ml). After stirring at room temperature for 30 minutes, methanol was evaporated off under reduced pressure, and the solid precipitated by addition of acetone to the residue which was washed with acetone, to give (N-γ-L-glutamyl-S-nitroso-D-penicillamyl)glycine (0.19 g).

Working Example 2 (Synthesis of the Compound 7)

To the solution of (N- $\gamma$ -L-glutamyl-D-penicillamyl)glycine hydrochloride (0.5 g) in methanol (5 ml), was added at 0°C the solution of ethyl nitrite in ethanol (10%) (1.1 ml). At the same temperature a drop of 4N-hydrochloric acid-methanol solution was added, and the mixture was stirred for 30 minutes. The solvent was evaporated off under reduced pressure, and the resultant crystals were washed with diethyl ether, to give (N- $\gamma$ -L-glutamyl-S-nitroso-L-penicillamyl)glycine hydrochloride (0.5 g).

In the same way, the Compounds 1 to 6, 9 to 11, and 13 to 34 listed in Table 2 shown below were synthesized.

Working Example 3 (Synthesis of the Compound 12)

To the solution of (N- $\beta$ -L-aspartyl-D-penicillamyl)glycine hydrochloride (0.2 g) in 1N-hydrochloric acid (0.56 ml) and water (1.0 ml), was added dropwise at room temperature the solution of sodium nitrite (0.077 g) in water (0.5 ml). The reaction mixture was stirred at room temperature for 30 minutes, loaded onto an LH-20 column, and eluted with water. The fractions containing the desired product were freeze-dried, to give (N- $\beta$ -L-asparagyl-S-nitroso-D-penicillamyl)glycine (0.2 g).

Table 2 shows the structure, physical properties, and NMR data of the Compounds 1 to 34 obtained in the Working Examples.

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	55		50	45	AF.	40	35	30	25	20	15	10	5
C C	Table	Ø 7		×	N.O N.O N.O N.O	>-							
Col	Compound	ınd	Configuration X of Pen Y	igurat:	ition en Y	I HA Ph	Molecular formula Physical properties Ex	Related Ex. No.	NMR ( $\delta$ ,	spectra ppm)in D20	I R (KI	IR(KBr)(cm <sup>-1</sup> )	-1)
	T	ж		<u> </u>	G1y-OH		C,H,3N3O,S.HCQ 44-48Tdecomp.	2	1.93(3H), 2.11 (2H), 4.81(1H)	1. 93(3H), 2. 11(3H), 4. 02 (2H), 4. 81(1H)		3800-2350, 1735, 1681, 1550-1510, 1400, 1380, 1320, 1215, 1130, 1040, 1015, 660	1681, 1380, 1040,
I	2	H-L-Glu-OH	Л и – ОН	Q	0 н	ت	C.oH.7N3OsS.HC@ amorphous	2	1.91(3H), -2.24(2H) (2H), 3.92	1. 91(3H), 1. 94(3H), 1. 96 -2. 24(2H), 2. 34-2. 61 (2H), 3. 92(1H), 5. 19(1H)	3700- 1515, 1126,	3700-2200, 1733, 1655, 1515, 1395, 1375, 1220, 1126, 990, 663	1655,
	က	H-D-C1n-OII	10-n1	<u> </u>	ОН	C1 63	C.oH.7NgOsS.HC@ 68-73°Cdecomp.	. 2	1.91(3H), -2.16(2H), (2H), 3.94	1. 91(3H), 1. 94(3H), 2. 02 -2. 16(2H), 2. 40-2. 53 (2H), 3. 94(1H), 5. 17(1H)	3800- 1515, 1128,	2200, 1735, 1650, 1395, 1375, 1220, 990, 665	1650,

	50 55		45	40	35	30	20 25	15	10	5
abl	le 2 (continued	nued	(							
				CaHisNa	N30sS		1.89(3H), 1.92(3H), 1.	1.97	3700-2250	0, 1740, 1655,
4	Ac	٦	Gly-0H	amo	amorphous	2	(3H), 3.87-3.98(2H),		1520, 1375	5, 1215, 1135,
							5.16(1H)		1035, 665	
				-						
				C12H2	C12H20N+07S.HCQ		1.88(3H), 1.98(3H), 1.	1.90	3800-2150,	, 1738, 1650,
ιΩ	H-L-Glu-011		Gly-0H	84-89	-89°decomp.	2	-2.22(2H), 2.30-2.è	, 29	1525, 1415	5, 1392, 1371,
							(2H), 3.81-3.99(3H),		1215, 1130	0, 1035, 665
							5.21(1H)			
				C12H20N+	0 N + O + S		1.90(3H), 1.99(3H),	1.90	3700-2400,	, 1640, 1520,
9	H-L-Glu-OH	<u>a</u>	G1y-0H	amo	amorphous		-2.13(2H), 2.26-2.6	5.5	1392, 1232	
	•						(2H), 3. 67(1H), 3. 77(2H)	7(2H)	$UV(H_2O): \lambda m$	max=
							5.21(1H)			340.0nm
				C12H2	C, 2H20N+O7S·HC@		1.89(3H), 1.98(3H),	1.90	3800-2200	0, 1738, 1650,
1	H-L-Glu-OH	Ω	G1y-0H	108-113°C	131	2	-2.16(2H), 2.40-2.5	56	1525, 1415,	, 1395, 1371,
- 3	-			-	decomp.		(2H), 3. 91(1H), 3. 93(2H)	3(2H)	1220, 1132,	,1034, 665
							5.20(1H)			

	50		45	40	35	30	20	15	10	5
Table	ole 2 (continued)	inue	(a)							
	l			CIZHZON	C, 2 H 2 0 N + O, S - HCQ		1. 90(3H), 1. 99(3H), 1.	), 1.90	3800-2200, 165	1650, 1520,
$\infty$	H-D-Glu-OH		G1y-0H	100-1050	2.5	2	-2.17(2H), 2.36-2.60	. 60	1395, 1313, 1235,	1235, 1130,
				де	decomp.		(2H), 3. 91(1H), 3. 94(2H)	94(2H)	665	
							5.21(1H)			
				CizHzol	C12H20N107S-HC2		1.91(3H), 2.01(3H), 2.00	), 2.00	3700-2300, 1720, 1660,	1720, 1660,
တ	H-L-Glu-	ب.	G1y-0H	98-1050		2	-2.24(2H), 2.30-2.60	. 60	1540, 1500, 1410, 1210,	1410, 1210,
		<del></del>	<del></del> -	дe	decomp.		(2H), 3. 95(2H), 4. 09(1H)	(11)60	665	
							5.27(1H)			
				C11H18N3O6S	130eS		1. 93(3H), 2. 01(3H), 2.	), 2.69	3700-2300,	1738, 1658,
10	H-L-Asp-OH	<u> </u>	G1y-OH	amorphous	snouc	က	-3.06(2H), 3.92-4.02	. 02	1526, 1385, 1218	1218
							(3H), 5.24(1H)		UV(H <sub>2</sub> O): Amax=	a X =
									•	336.8nm
				CIIHIBA	C H. & N3O6S·HCQ		1,87(3H), 1,96(3H), 2.	), 2.80	3700-2200,	1736, 1653,
=	H-L-Asp-OH		G1y-0H	95-100%		2	-3.09(2H), 3.80-4.04	. 04	1535, 1210,	665
				ď	decomb.		(2H), 4. 27(1H), 5. 18(1H)	18(1H)		
		· ·								
	•									

Table 2 (continued)    C	О	35	30	20 25	15	10	5
-L-Glu-OH L L-Ala-OH -L-Glu-OH L L-Val-OH							
H-L-Glu-OH L L-Ala-OH II-L-Glu-OH L L-Val-OH II-L-Glu-OH D L-Val-OH		C. 3 H 2 2 N + O 7 S • H C 2		1. 37(3H), 1. 91(3H), 2. 01	1 3700-2200,	1730, 165	50,
-L-G u-O   L L-Val-O		.07-112°C	2	(3H), 1. 90-2. 17(2H),	1520, 1455, 139	1390, 1370,	
II-L-Glu-OH L L-Val-OH		decomb.		2. 39-2. 55(2H), 3. 92(1H)	1218, 1150,	835, 66	10
-L-Glu-OH				4. 23-4. 38(1H), 5. 18(1H)			
II-L-Glu-OH L L-Val-OH	-	C.sHzeN+D,S.HC@		0.86(3H), 0.89(3H), 1.89	9 3700-2250,	1725, 165	0
H-L-Glu-OH D L-Val-OH		18-122t	2	(3H), 1, 98(3H), 0, 80	1520, 1394, 1372, 1220	1372, 122	
H-L-Glu-OH D L-Val-OH		decomp.		2. 23(3H), 2. 37-2. 58(2H)	) 1145, 1128,	665	
H-L-Glu-OH D L-Val-OH		o		3. 91(1H), 4. 12-4. 23(1H)			
H-L-Glu-OH D L-Val-OH				5.25(1H)			
H-L-Glu-OH D L-Val-OH 112-	0	1, 5 H 2 & N + O , S - HCQ		0.87(3H), 0.91(3H), 1.90	0 3700-2250,	1738, 1650,	
decomp.		12-117°C	2	(3H), 1.96(3H), 1.95-	1522, 1392,	1370, 1220,	
		decomp.		2. 23(3H), 2. 34-2. 54	1145, 6,68		
	<u> </u>			(2H), 3. 90(1H), 4. 07-			
1				4.26(1H), 5.30(1H)	•		
C, sH2 sN4 O, S. HCQ	0	1 6 H 2 8 N + O 7 S - HC@		0.70-0.92(6H), 1.46-	3700-2200,	1725, 164	<u>ئ</u>
15 H-L-Glu-OH L L-Leu-OH 120-124C		20-124C	7	1.73(3H), 1.79-2.19	1520, 1390, 1370,	122	ي.
, decomp.		decomp.		(2H), 1.89(3H), 1.97(3H)	) 1210, 1150,	665	
				2. 35-2. 60(2H), 3. 89(1H)			
9				4. 25-4. 40(1H), 5.17(1H)			

· ( ) : : : : : : : : : : : : : : : : : :	5 (		35	30	25	0	10	5
nnec		1	C. s H 2 1 N 1 0 , S - H C @	,	1.87(3H), 2.02(3H), 1.	02(3H), 1.64	3650-2200, 1740,	40, 1625,
H-L-Glu-OH	L-Pro-01	120-1	25c decomp.	2	-2. 52(8H), (3H), 3. 86(	-2, 52(8H), 3, 68-3, 93 (3H), 3, 86(1H), 5, 56(1H)	1505, 1450, 1210, 1190, 665	10, 11, 0, 11, 20, 11, 20, 11, 20, 20, 20, 20, 20, 20, 20, 20, 20, 20
-		CiaHze	C H 2 6 N + O , S · HCQ		1.74(3H), 1.	1. 74(3H), 1.87(3H), 1.90	3800-2200, 1730, 1650,	730, 1650,
T -G1 u - OH.   T	L-Phe-OH	122-1270	٦, ٢	2	-2.19(2H), 2.21-2.50	2. 21-2. 50	1520, 1459, 1	1395, 1374,
		ซ้	decomb.		(2H), 2.75-2.98(1H),	2.98(1H),	1225, 1132,	703
					3, 08-3, 28(	08-3.28(1H), 3.89(1H)		
				1	4.55-4.70(	55-4.70(1H), 5.10(1H)		
					7.06-7.40(5H)	5H)		
		C19H26	C. 9 H 2 6 N + O 8 S - H C @		1.76(3H), 1	1. 76(3H), 1. 86(3H), 1. 94	3800-2200, 1	1730, 1650,
H-L-Glu-OH L	L-Tyr-OH	107-112T	2.C	2	-2.14(2H), 2.20-2.46	2, 20-2, 46	1518, 1450, 1395, 1375,	395, 1375,
		d€	decomp.		(2H), 2.77(	(2H), 2. 77(1H), 3. 15(1H)	1230, 1130, 1110,	110, 835,
					3.87(1H), 4	3.87(1H), 4.55-4.70(1H)	670	
					5.08(1H), 6.70(2H),	.70(2H),		
					7.03(1H)			

55	50	<b>4</b> 5	45	40	35	30	25	20	15	10	5
7	able 2 (continued	ued									
1 8	H-L-Glu-0II		L-Glu-OR	C15H2+	N.O.S.HC@decomp.	2	1.88(3H), 1.97(3H), 1.70 -2.50(8H), 3.90(1H), 4.39(1H), 5.17(1H)	7(3H), 1.70 90(1H), 7(1H)	3800-2230, 1520, 1455, 1220, 1135,	1730, 1395, 665	1855,
20	H-L-Glu-OH		NHCHPh <sub>2</sub>	C23	H28N.OsS.HC@ -130° decomp.	2	*1.91(3H), 1.96(3H), 2.20-2.57(4H), 3.40(1H), 3.82(1H), 5.46(1H), 6.18 (1H), 7.18-7.40(10H), 8.40(3H), 8.62(1H), 9.51	.91(3H), 1.96(3H), 20-2.57(4H), 3.40(µH) 82(1H), 5.46(1H), 6.18 H), 7.18-7.40(10H), 40(3H), 8.62(1H), 9.51	3700-2150, 1520, 1458, 1232, 1125,	1740, 1393, 1032,	1650, 1372, 702
						.,-	(1H)				
21	H-L-Glu-OH		L-Asp-OH	C + H 84-	2.1M.O.S.HCW 88t decomp.	27	1. 92(3H), 2. 00(3H), 2. -2. 19(2H), 2. 42-2. 55 (2H), 2. 86-2. 96(2H), 3. 93(1H), 4. 72(1H), 5. (1H)	0(3H), 2. 02 42-2. 55 96(2H), 2(1H), 5. 20	3700-2200, 1525, 1225,	00, 1735, 25, 670	1650,
22	H-L-Glu-OH		N- 1 = K-7	C15H25N+O7S.HCQ 104-109T decomp.	0,8.HC@	2	1. 82-2. 26(4H), 1. 92(3H), 2. 01(3H), 2. 03(3H), 2. 37-2. 66(4H), 3. 95(1H), 4. 54(1H), 5. 20(1H)	), 1. 92(3H) 03(3H), 2. 3. 95(1H), 0(1H)	3700-2200, 1520, 1225,	670	1650,

5																				,
		1650,						45,						İ	<del>ر</del> 5,	25,				
		16						16							16	12				
		30,	670					35,	700						30,	70,				
10		1730,	9					17	7						1730, 1645,	3				
			0					0,	0					Ì		Ô				
		-2200,	122					2 2 0	123						220	139				
		0	1520, 1220,					3700-2200, 1735, 1645,	1520, 1230,						3700-2200,	520, 1390, 1370, 122	2			
15		370	52				!	7 0	5.2					-	7 0	52	665			
																<u>.</u>				
		0.82(3H), 0.88(3H), 1.22		77-2. 24(3H), 1. 91(3H)						2.44(2H), 3.60(1H), 3.8	(1H), 5. 45(1H), 6. 17(1H)	2	(3H), 8, 56(1H), 9, 49(1H)			1.76(3H), 1.92(3H), 1.96		2. 43-2. 61(2H), 3. 95(1H)		
		1'	<u>-</u>	) [	53	4		9 1	9	 ∾	7 (		) 6		10			) 2 (	$\bigcirc$	
20		3H)	$\exists$	7	-2.	4. 2			2. 2	(H)	6. 1	φ.	9.4	-	1.4	3H)	(2H	es.	(18	
		) &	53	$\overline{\Box}$	41	$\sim$	$\overline{}$	H)	$\sim$	)(	~	0 H	~	ļ	~	5	20	~	27	ĺ
		8.	<u>-</u> ;	(3H	2.	(TH	$\mathbb{H}$	)(3	(31	3.6	3	3(1	E)		(6 H	. 9	-2.	(2 H	ა.	- {
		<u>`</u>	(1H), 1.27-1.53(1H),	24	, 1. 99(3H), 2. 41-2. 53	(2H), 3.94(1H), 4.24	(1H), 5. 25(1H)	*1.80-2.20(2H), 1.	(3H), 1.96(3H), 2.26-	~	<del>4</del> 5	,7.20-7.43(10H),8.32	56		0.75-1.01(6H), 1.45	~	(3H), 2.06-2.20(2H),	61(	, 4.30(1H), 5.27(1H)	
25		(3H	_;	-2.	3(3	က်	5.	7-0	ij	2 H	ic.	1-7	∞.		<del>_</del> ;	3 H	2.	.2	$\Box$	ĺ
		82(	$\widehat{\Xi}$	-11	6	Ε,	Ξ,	8	$\Xi$	44(	Ξ,	50	Η),		75	9/	Ê	-63	30	
		· .	こ	_;		(2	$\Box$	*	3	2:		. 7	(33	ŀ	· .		(3)	2.	4.	]
					·															
30		ĺ	2					8	-2						~~	2				
		C. 6. H. 2 8 N. 4 O. S. HC						H28N+OsS+HCQ							C18 H28 N+07S.HC@					
		S.		decomp.			i	S.		ď.					Ś		ġ			
35		0,	چ	00				0	د۽	decomb					Ó	ر۽	decomb			
		N 8 3	15	de				¥.	5.5	de(				ľ	₩ 8	36	Sec			
		вЯз	109-115C					3 H 2	150-155T						в Н 2	130-136T	Ö			
		C1	10					C23	15						ပ်	13				
40			<u>=</u>						р.							HC				$\dashv$
			L-Ile-0E						NHCHPh 2							L-Leu-OH				
			$\overline{}$						NHC							-Le				
	<u> </u>		<u> </u>			-										<u> </u>				
45	(continued		_						Q											
	-i-																		<del></del>	
	'nt	ċ	n -0						L-Glu-0H							-L-G1u-OH				İ
50	00)	L .	<u>, , , , , , , , , , , , , , , , , , , </u>					. l	n					Ì	L	n l				
	2		19-7						J-7							, -G				1
		· 	<u>-</u> H						] H							H-L				
	Table				•									-						
55	Ta		23						24							25				_

50	45	35	30	20	10
2 (continued)	nued)				
		C19H25N+0,S.HCQ	2	1. 63(6H), 1. 89-2. 25	3700-2200, 1730, 1650,
L-Glu-0H	D L-Phe-OH	1H 120-125℃	2	(2H), 2, 30-2, 66(2H),	1520, 1455, 1390, 1370,
		decomp.		2.94(1H), 3.18-3.43	1220, 1125, 700, 665
				(1H), 3.91(1H), 4.63-	
				4.70(1H), 5.12(1H),	
		:		7.05-7.50(5H)	
1		C15H2+N+O9S.HC0		0.80-2.27(4H), 1.92	3700-2200, 1730, 1650,
T-Glu-OH	D L-Glu-OH	H 91-96°C	2	(3H), 1. 97 (3H), 2. 34-	1520, 1220, 665
		decomp.		2.64(4H), 3.95(1H),	
				4.34(1H), 5.25(1H)	
		C13H23N4O8S.HC2		1.94(3H), 2.03(3H),	3800-2200, 1735, 1650,
L-Glu-0H	L L-Ser-OH	H 89- 92°C	2	2.05-2.22(2H), 2.42-	1520, 1390, 1370, 1225,
		decomb.		2.55(2H), 3.79-4.02	1135, 1070, 665
				(3H), 4. 52(1H), 5. 29(1H)	
<u></u>		C15H2+N+07S-HC0		1.87(3H), 1.90-2.36	3700-2200, 1735, 1630,
-G1u-OH	D L-Pro-OH	H 77-81°C	7	(6H), 2.01(3H), 2.43-	1510, 1450, 1220, 1190,
		decomb.		2.57(2H), 3.68-3.89	665
				(2H), 3.96(1H), 4.32	
: : :		,		(1H), 5.64(1H)	

	1650,	670						1655,	1120,						1 1	,000,	210,		
	_	835,						1735,	1180,	680					6	1740,1	1390, 1		
	3700-2200,	1515, 1220,						3700-2200,	1520, 1215,	1035, 1005,						3/50-2200,	1535, 1410,	1130, 660	
	9 6					8		6 9							į į				
	1,87(3H),1.	, 2. 31-2. 43	-2.92(1H),	(1H), 3.90	-4.70(1H),	5.11(1H), 6.	(2H)	1.89(3H), 1.	, 2. 31-2. 43	-2.97(1H),	(1H), 3.93	-4.73(1H),	7. 28-7. 43	-7.78(2H)		Z. 00(3H), Z.	3.97(2H),	5.24(1H)	
	1.77(3H),	-2.12(2H)	(2H), 2.76	3, 10-3, 26	(1H), 4.51	4.64(2H),	(2H), 7.13	1.79(3H),	-2.21(2H)	(2H), 2.82	3.06-3.19	(1H), 4.52	5.13(1H),	(2H), 7. 59		1.91(3H),	-3.14(2H),	4.24(1H),	
		2							2								2		
	C2, H28N+O, oS.	нсд	108-112°C	decomp.				C19H26N4O10S2.	нсе	140-145°C	decomb.					C11H18N+U7S-HC	85- 900	decomp.	
	CH 2 COOM	-Tyr-OH						SO H	L-Phe-OH		-						G1y-0H		
ned)		 							0 7										
2	L	НО-119-7-Н						[	H-L-Glu-011							L	H-L-Asp-OH		Service servic
Tab]		30							31		-						32		
	Table 2 (continued)	2 (continued)  CH <sub>2</sub> COOH C <sub>2</sub> .H <sub>2</sub> 8N <sub>+</sub> O <sub>1</sub> o <sub>S</sub> · 1.77(3H), 1.87(3H), 1.9	2 (continued)  -L-Glu-OH   L-Tyr-OH   HCQ   2   -2.12(2H), 2.31-2.43   1515,1220, 835,	2 (continued)  -L-Glu-OH   L-Tyr-OH   HC&   2 -2.12(2H), 2.31-2.43   1515,1220, 835,   108-112t   (2H), 2.76-2.92(1H),	2 (continued)  CH <sub>2</sub> COOH C <sub>2</sub> .H <sub>2</sub> 8N <sub>+</sub> O <sub>1,o</sub> S·	2 (continued)  -L-Glu-OH	2 (continued)  L CH <sub>2</sub> COOH C <sub>2</sub> :H <sub>2</sub> 8N <sub>+</sub> O <sub>1,o</sub> S· 1.77(3H), 1.87(3H), 1.96 3700-2200, 1735, 1-101 HCQ 2.12(2H), 2.31-2.43 1515, 1220, 835, 108-112° (2H), 2.76-2.92(1H), 3.90 (1H), 4.51-4.70(1H), 6.82	2 (continued)  -L-Glu-OH	2 (continued) -L-Glu-OH	2 (continued)  L L-Tyr-OH	2 (continued)  -L-Glu-OH L L-Tyr-OH HCQ 2 -2.12(2H), 2.31-2.43 1515,1220, 835,  -L-Glu-OH L L-Tyr-OH HCQ 2 -2.12(2H), 2.76-2.92(1H),  decomp. 3.10-3.26(1H), 3.90  (1H), 4.51-4.70(1H),  4.64(2H), 5.11(1H), 6.82  -L-Glu-OH L DL-Phe-OH HCQ 2 -2.21(2H), 1.89(3H), 1.95 3700-2200, 1735, 11  -L-Glu-OH L DL-Phe-OH HCQ 2 -2.21(2H), 2.31-2.43 1520, 1215, 1180, 11  -L-Glu-OH L DL-Phe-OH HCQ 2 -2.21(2H), 2.31-2.43 1520, 1215, 1180, 11	2 (continued)  -L-Glu-OH L L-Tyr-OH HCQ 2 -2.12(2H), 1.87(3H), 1.96 3700-2200, 1735, 1  -L-Glu-OH L L-Tyr-OH HCQ 2 -2.12(2H), 2.31-2.43 1515, 1220, 835, decomp.  3.10-3.26(1H), 3.90  (1H), 4.51-4.70(1H), 4.682  (2H), 7.13(2H)  -L-Glu-OH L DL-Phe-OH HCQ 2 -2.12(2H), 1.89(3H), 1.95 3700-2200, 1735, 1 decomp.  14.64(2H), 7.13(2H)  -L-Glu-OH L DL-Phe-OH HCQ 2 -2.21(2H), 2.31-2.43 1520, 1215, 1180, 1 decomp.  3.06-3.19(1H), 3.93	2 (continued)  -L-Glu-OH	2 (continued)  -L-Glu-OH L L-Tyr-OH HCg 2 -2.12(2H), 2.31-2.43 1515,1220, 835, -L-Glu-OH L L-Tyr-OH HCg 2 -2.12(2H), 2.31-2.43 1515,1220, 835, -L-Glu-OH L L-Tyr-OH HCg 3.10-3.26(1H), 3.90  (1H), 4.51-4.70(1H), 6.82  (2H), 7.13(2H)  -L-Glu-OH L DL-Phe-OH HCg 2 -2.21(2H), 1.89(3H), 1.95 3700-2200, 1735, 1 1 79(3H), 1.89(3H), 1.95 3700-2200, 1735, 1 1 140-145°C (2H), 2.82-2.97(1H), 3.93  decomp. 3.06-3.19(1H), 3.93  (1H), 4.52-4.73(1H), 5.93	2 (continued)  -L-Glu-OH	2 (continued)  -L-Glu-OH	2 (continued)  -L-Glu-OH L L-Tyr-OH HCg 2 -2.12(2H), 2.31-2.43 1515,1220, 835, 10-61u-OH L L-Tyr-OH HCg 3.10-2.26(1H), 3.90  -L-Glu-OH L L-Tyr-OH HCg 3.10-3.26(1H), 3.90  -L-Glu-OH L DL-Phe-OH HCg (2H), 7.13(2H)  -L-Glu-OH L DL-Phe-OH HCg 2 -2.21(2H), 2.31-2.43 1520,1215,1180, 1140-145°  -L-Glu-OH L DL-Phe-OH HCg 2 -2.21(2H), 2.31-2.43 1520,1215,1180, 1140-145°  -L-Glu-OH L DL-Phe-OH HCg 2 -2.21(2H), 2.31-2.43 1530,105, 680  -L-Glu-OH L DL-Phe-OH HCg 2 -2.21(2H), 2.31-2.43 1530,105, 680  -L-Glu-OH L DL-Phe-OH HCg 2 -2.21(2H), 2.31-2.43 1530,105, 680  -L-Glu-OH L DL-Phe-OH HCg 2 -2.21(2H), 2.31-2.43 1530,105, 680  -L-Glu-OH L DL-Phe-OH HCg 2 -2.21(2H), 2.31-2.43 1530,105, 680  -L-Glu-OH L DL-Phe-OH HCg 2 -2.21(2H), 2.31-2.43 1530-2200,1740,1	2 (Continued)  -L-Glu-OH	2 (continued)  -L-Glu-OH

5	1735, 1650, 1115, 660	1735, 1680, 1400, 1315,
10	3800-2200, 1735, 1520, 1210, 1115,	3800-2200, 1735, 1680, 1540, 1505, 1400, 1315, 1200, 655
15 20	(3H), 2.06 1-2.55 5.19(1H)	
25	1. 93(3H), 1. 96(3H), 2. 06 3800-2200, 1735, 1650, -2. 18(2H), 2. 44-2. 55 1520, 1210, 1115, 660 (2H), 3. 98(1H), 5. 19(1H)	1. 95(3H), 2. 12(3H), 4. 05 (2H), 4. 83(1H)
30	2	2
35	C.oH.7NoOsS.HCQ 73-80°C decomp.	C, H, 3 N3 O + S · HCQ 63 - 68°C decomp.
45	НО	G 1 y - OH
),ued)		
rable 2 (continued	II-L-Glu-0II	T.
Table	က	34

аs isolated 34 were 9, and respective hydrochlorides. 10 Compounds

the 35  $\ast$  ; measured by using DMSO-d $_6$  as the solvent and TMS internal standard.

### Preparation Examples

### Preparation Example 1

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- (1) Compound 1 2 g
- (2) lactose 196 g
- (3) corn starch 50 g
- (4) magnesium stearate 2 g
- (1), (2) and 20 g of corn starch were mixed and granulated together with a paste made from 15 g of corn starch, to which 15 g of cornstarch and (4) were added. The mixture was compressed with a compress-tableting machine, to produce 2000 tablets of 3 mm in diameter containing 1 mg of (1) in each tablet.

### Preparation Example 2

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- (1) Compound 2 4
- (2) lactose 194 g
- (3) corn starch 40 g
- (4) magnesium stearate 2 g
- (1), (2) and 15 g of corn starch were mixed and granulated together with a paste made from 15 g of corn starch, to which 10 g of corn starch and (4) were added. The mixture was compressed with a compress-tableting machine, to produce 2000 tablets of 5 mm in diameter containing 2 mg of (1) in each tablet.

## Preparation Example 3

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- (1) Compound 1 100 mg
- (2) Avicel (crystalline cellulose) 300 mg
- (3) lactose 595 mg
- (4) magnesium stearate 5 mg
- (1), (2), (3) and (4) described above were mixed thoroughly, and compressed directly with a compress-tableting machine, to produce 100 sublingual tablets (3 mm in diameter) containing 1 mg of (1) in each tablet.

# Experimental Example 1

In a 20 ml-tank (37°C, aerated with 95%  $O_2$  + 5%  $CO_2$ , pH7.4), a specimen (pig left coronary descending artery (LAD), or rat aorta) was suspended. The specimen was allowed to contract by addition of  $PGF_{2\alpha}$  (6  $\mu$ M) for pig coronary artery or KCl (60 mM) or TEA (45 mM) + Ba (0.3 mM) for rat aorta, and then a test compound was added at a time or cumulatively; the relaxing effect of the compound on the constrictive tension was examined; the Compounds 1 and 2 showed a powerful relaxing effect.

# Experiment Example 2

# Relaxing effects on KC1 induced contraction in isolated rat aorta

Ring preparations of rat thoracic aorta were placed in  $20m\ell$  organ baths containing Krebs-Hemseleit solution kept at 37°C, a pH of 7.4 and gassed with 95%  $CO_2$  - 5%  $O_2$ . After steady state contraction induced by 60mM KC1, vasorelaxing effects of test compounds ( $10^{-6}$ ,  $10^{-7}$  mol/l) were examined. The vasorelaxing effects were expressed as % relaxation from the maximum contraction induced by 60mM KC1. The relaxing effects are shown in Table 3.

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	Table			Retension		
5	Compound	10-11	etension time/min	10-e 71	time/min	
	2	18	24	6 2	> 30	
10	3	19	17	ã 0	> 30	
	5	16	25	4 7	> 30	
	7	1.1	> 30	64	> 30	
15	1 1	1 2	2 0	37 .	> 30	
70	13	19	> 30	85	> 30	
	1.4	11 -	12	7 4	> 30.	
20	17	2,0	1 7	66	> 30	
	19	19	2 0	58	> 30	
	24	26	> 30	75	> 30	
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Claims

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Claims for the following Contracting States : AT, BE, CH, DE, DK, FR, GB, GR, IT, LI, LU, NL, SE

1. A compound of the formula:

$$X' - \frac{R'}{N}$$
 CII -  $\frac{R'}{C}$  SNO

wherein  $R^1$  and  $R^2$  are independently a hydrogen atom or a hydrocarbon residue which may be substituted;  $R^3$  is a hydrogen atom, an acyl group or a hydrocarbon residue which may be substituted;  $X^1$  is a hydrogen atom, an acyl group, a lower alkoxy group or a hydrocarbon residue which may be substituted;  $X^2$  is an acyl group or a carboxyl group which may be esterified or which may form an amide; with a proviso that when  $X^2$  is a carboxyl group  $X^1$  is not a hydrogen atom or acetyl group and that when both  $R^1$  and  $R^2$  are hydrogen atoms  $X^1$  is not an acetyl group or  $\gamma$ -glutamyl group, or a salt thereof.

- 2. A compound according to claim 1, wherein R<sup>1</sup> and R<sup>2</sup> are independently a hydrocarbon residue which may be substituted, or R<sup>1</sup> and R<sup>2</sup> may be bound to each other to form a ring of the formula: -(CH<sub>2</sub>)<sub>n</sub>- wherein n is an integer of 2 to 6.
  - 3. A compound according to claim 1, wherein X1 is an amino acid derived acyl.
- 4. A compound according to claim 1, wherein R¹ and R² are independently a hydrocarbon residue which may be substituted; R³ is a hydrogen atom, an acyl group or a hydrocarbon residue which may be substituted; X¹ is an amino acid derived acyl; X² is an acyl group or a carboxyl group which may be esterified or which may form an amide.

- A compound according to claim 1, wherein the hydrocarbon residue represented by R1, R2, R3 or X1 is a chain saturated, chain unsaturated, cyclic saturated or cyclic unsaturated hydrocarbon residue, each of which may be substituted by one to three groups selected from the class consisting of halogen atom, nitro, nitrile, hydroxyl, carboxyl, C1-4 alkoxy, C1-4 alkylthio, amino, mono- or di-C1-4 alkyl amino, mono- or diaralkylamino, mono- or di-pyridylamino, C<sub>1-4</sub> alkoxycarbonyl, cyclo C<sub>3-6</sub> alkylcarbonyl, carbamoyl, monoor di- $C_{1-4}$  alkylcarbamoyl, and phenyl, phenoxy, benzoyl, phenoxycarbonyl, phenyl  $C_{1-4}$  alkylcarbamoyl or phenylcarbamoyl group, in which each of said phenyl group may be substituted by 1 to 4 groups selected from the class consisting of C<sub>1-4</sub> alkyl, halogen atom, hydroxyl, benzyloxy, amino, mono- or di-C<sub>1-4</sub> alkyl-10 lamino, niro and C<sub>1-4</sub> alkoxycarbonyl.
  - A compound according to claim 1, wherein the acyl group represented by R3, X1 or X2 is a carboxylic, carbamic, sulfonic or oxycarboxylic acyl group, each of which may be substituted by one to three groups selected from the class consisting of halogen atom, nitro, nitrile, hydroxyl, carboxyl, C<sub>1-4</sub> alkoxy, C<sub>1-4</sub> alkylthio, amino, mono- or di-C<sub>1-4</sub> alkyl amino, mono- or di-aralkylamino, mono- or di-pyridylcarbonylamino, C<sub>1-6</sub> alkylcarbonyl, C<sub>1-4</sub> alkoxycarbonyl, cyclo C<sub>3-6</sub> alkylcarbonyl, carbamoyl, mono- or di-C<sub>1-4</sub> alkylcarbamoyl, and phenyl, phenoxy, benzoyl, phenoxycarbonyl, phenyl C<sub>1-4</sub> alkylcarbamoyl or phenylcarbamoyl group, in which each of said phenyl may be substituted by 1 to 4 groups selected from the class consisting of C<sub>1-4</sub> alkyl, halogen atom, hydroxyl, benzyloxy, amino, mono- or di-C<sub>1-4</sub> alkylamino nitro and C<sub>1-4</sub> alkoxycarbonyl.
  - A compound according to claim 1, wherein the lower alkoxy group is  $C_{1-6}$  alkoxy group.
  - A compound according to claim 1, wherein the carboxyl group which may be esterified is carboxyl or a group of the formula: -CO-OR5 wherein R5 is a hydrocarbon residue which may be substituted.
  - A compound according to claim 1, wherein the carboxyl group which may form an amide is carboxyl or a group of the formula:

$$-CO-N \binom{R^6}{R^7}$$

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wherein R<sup>6</sup> is a hydrogen atom or a hydrocarbon residue which may be substituted, and R<sup>7</sup> is a hydrogen atom or a lower alkyl group or  $R^6$  and  $R^7$  may form a cyclic amino group together with the adjacent nitrogen atom.

- 40 10. A compound according to Claim 1, wherein R1 and R2 are independently a chain saturated or cyclic unsaturated hydrocarbon residue, or R1 and R2 together with the adjacent carbon atom form cyclopentyl or cyclohexyl.
  - 11. A compound according to claim 1, wherein R1 and R2 are independently C1-8alkyl group.
  - 12. A compound according to claim 1, wherein R<sup>1</sup> and R<sup>2</sup> are methyl.
  - 13. A compound according to claim 1, wherein R3 is a hydrogen atom or an acyl group.
- 14. A compound according to claim 13, wherein the acyl group is C<sub>1-8</sub> alkyl carbonyl or C<sub>8-10</sub> aryl carbonyl. 50
  - 15. A compound according to claim 1, wherein R3 is a hydrogen atom.
  - 16. A compound according to claim 1, wherein X1 is a hydrogen atom or an acyl group.
- 55 17. A compound according to claim 16, wherein the acyl group is an amino acid derived acyl group.
  - 18. A compound according to claim 17, wherein the amino acid is glycine, alanine, glutamic acid, leucine, isoleucine, phenylalanine, aspartic acid, cysteine, sarcosine, glutamine, asparagine or proline.

- 19. A compound according to claim 17, wherein the amino acid is glycine, aspartic acid, asparagine, glutamic acid, glutamine or phenylalanine.
- 20. A compound according to claim 17, wherein the amino acid is glutamic acid or aspartic acid.
  - 21. A compound according to claim 1, wherein X2 is a carboxyl group which may be esterified.
  - 22. A compound according to claim 1, wherein X2 is a carboxyl or carbamic acyl group.
- 23. A compound according to claim 22, wherein the carbamic acyl group is carbonyl amino or a carboxyl group forming an amide with an amino acid.
  - 24. A compound according to claim 23, wherein the amino acid is glycine, alanine, glutamic acid, leucine, isoleucine, phenylalanine, aspartic acid, cysteine, sarcosine, glutamine, asparagine or proline.
  - 25. A compound according to claim 23, wherein the amino acid is glycine, aspartic acid, asparagine, phenylalanine, glutamic acid or glutamine.
  - 26. A compound according to claim 1, wherein R¹ and R² are independently C₁-6 alkyl, phenyl or naphthyl, or R¹ and R² form cyclopentyl or cyclohexyl together with the adjacent carbon atom; R³ is a hydrogen atom or a C₀-10 aromatic acyl group; X¹ is a hydrogen atom or an amino acid derived acyl group in which said amino acid is selected from the group consisting of glycine, aspartic acid, phenylalanine, asparagine, glutamic acid and glutamine; X² is a carboxyl group, carbonylamino or a carboxyl group forming an amide with an amino acid residue in which said amino acid is selected from the group consisting of glycine, aspartic acid, phenylalanine, asparagine, glutamic acid and glutamine.
    - 27. A compound according to claim 1, wherein the salt is a pharmaceutically acceptable salt.
    - 28. A compound according to claim 1, which is N-(N-L-γ-Glutamyl-D-penicillamyl)glycine.
- 29. A compound according to claim 1, which is N-(N-L-γ-Glutamyl-L-penicillamyl)-L-valine.
  - 30. A compound according to claim 1, which is N-(N-L-γ-GlutamyI-L-penicillamyI)-L-phenylalanine.
  - 31. A compound according to claim 1, which is N-(N-L-γ-Glutamyl-L-penicillamyl)-L-glutamic acid.
  - 32. A compound according to claim 1, which is N-(N-L-γ-Glutamyl-D-penicillamyl)diphenylmethylamine.
  - 33. A pharmaceutical composition suitable for the therapy or prophylaxis of hypertension or angina pectoris which comprises (a) as the active ingredient, an effective amount of a compound according to claim 1 or a salt thereof and (b) a pharmaceutically acceptable carrier, excipient or diluent therefor.
    - 34. The use of a compound according to claim 1 or a salt thereof for the preparation of a medicine for the therapeutic treatment of a mammal.
  - 35. A method for producing a compound of the formula (I):

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$$X' - \frac{R^3}{N}$$
  $CH - \frac{R^4}{C} - SNO$ 

wherein  $R^1$  and  $R^2$  are independently a hydrogen atom or a hydrocarbon residue which may be substituted;  $R^3$  is a hydrogen atom, an acyl group or a hydrocarbon residue which may be substituted;  $X^1$  is a hydrogen atom, an acyl group, a lower alkoxy group or a hydrocarbon residue which may be substituted;  $X^2$  is an acyl group or a carboxyl group which may be esterified or which may form an amide; with a proviso that when  $X^2$  is a carboxyl group  $X^1$  is not a hydrogen atom or acetyl group and that when both  $R^1$  and  $R^2$  are hydrogen atoms  $X^1$  is not acetyl group or  $\gamma$ -glutamyl group, or a salt thereof, which comprises.

(a) subjecting a compound of the formula (II):

$$X_{1} - \frac{1}{N} > CH - \frac{1}{C} - SH$$

wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $X^1$  and  $X^2$  are the same as described above to the nitrosation reaction, and, if desired,

(b) converting a product obtained by the above process (a) into a salt thereof.

# 15 Claims for the following Contracting State: ES

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1. A method for producing a compound of the formula (I):

$$-X^{1} - \frac{R^{2}}{N} > CH - \frac{R^{1}}{C} - SNO$$

wherein R¹ and R² are independently a hydrogen atom or a hydrocarbon residue which may be substituted; R³ is a hydrogen atom, an acyl group or a hydrocarbon residue which may be substituted; X¹ is a hydrogen atom, an acyl group, a lower alkoxy group or a hydrocarbon residue which may be substituted; X² is an acyl group or a carboxyl group which may be esterified or which may form an amide; with a proviso that when X² is a carboxyl group X¹ is not a hydrogen atom or acetyl group and that when both R¹ and R² are hydrogen atoms X¹ is not acetyl group or -glutamyl group, or a salt thereof, which comprises.

(a) subjecting a compound of the formula (II):

$$\chi_1 - \frac{\chi_2}{N} > C \Pi - \frac{1}{C} - S \Pi$$

wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $X^1$  and  $X^2$  are the same as described above to the nitrosation reaction, and, if desired,

- (b) converting a product obtained by the above process (a) into a salt thereof.
- 2. A method according to claim 1, wherein R¹ and R² are independently a hydrocarbon residue which may be substituted, or R¹ and R² may be bound to each other to form a ring of the formula: -(CH₂)<sub>n</sub>- wherein n is an integer of 2 to 6.
  - 3. A method according to claim 1, wherein  $X^1$  is an amino acid derived acyl.
- 4. A method according to claim 1, wherein R¹ and R² are independently a hydrocarbon residue which may be substituted; R³ is a hydrogen atom, an acyl group or a hydrocarbon residue which may be substituted; X¹ is an amino acid derived acyl; X² is an acyl group or a carboxyl group which may be esterified or which may form an amide.
- 5. A method according to claim 1, wherein the hydrocarbon residue represented by R¹, R², R³ or X¹ is a chain saturated, chain unsaturated, cyclic saturated or cyclic unsaturated hydrocarbon residue, each of which may be substituted by one to three groups selected from the class consisting of halogen atom, nitro, nitrile, hydroxyl, carboxyl, C¹-4 alkoxy, C¹-4 alkylthio, amino, mono- or di-C¹-4 alkyl amino, mono-or di-aralkyla-

mino, mono- or di-pyridylamino,  $C_{1-4}$  alkoxycarbonyl, cyclo  $C_{3-6}$  alkylcarbonyl, carbamoyl, mono- or di- $C_{1-4}$  alkylcarbamoyl, and phenyl, phenoxy, benzoyl, phenoxycarbonyl, phenyl  $C_{1-4}$  alkylcarbamoyl or phenylcarbamoyl group, in which each of said phenyl group may be substituted by 1 to 4 groups selected from the class consisting of  $C_{1-4}$  alkyl, halogen atom, hydroxyl, benzyloxy, amino, mono- or di- $C_{1-4}$  alkylamino, niro and  $C_{1-4}$  alkoxycarbonyl.

- 6. A method according to claim 1, wherein the acyl group represented by R³, X¹ or X² is a carboxylic, carbamic, sulfonic or oxycarboxylic acyl group, each of which may be substituted by one to three groups selected from the class consisting of halogen atom, nitro, nitrile, hydroxyl, carboxyl, C¹-₄ alkoxy, C¹-₄ alkylthio, amino, mono- or di-C¹-₄ alkyl amino, mono- or di-aralkylamino, mono- or di-pyridylcarbonylamino, C¹-₃ alkylcarbonyl, C¹-₄ alkoxycarbonyl, cyclo C₃-₃ alkylcarbonyl, carbamoyl, mono- or di-C¹-₄ alkylcarbamoyl, and phenyl, phenoxy, benzoyl, phenoxycarbonyl, phenyl C¹-₄ alkylcarbamoyl or phenylcarbamoyl group, in which each of said phenyl groups may be substituted by 1 to 4 groups selected from the class consisting of C¹-₄ alkyl, halogen atom, hydroxyl, benzyloxy, amino, mono- or di-C¹-₄ alkylamino nitro and C¹-₄ alkoxycarbonyl.
  - 7. A method according to claim 1, wherein the lower alkoxy group is  $C_{1-6}$  alkoyl group.

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- 8. A method according to claim 1, wherein the carboxyl group which may be esterified is carboxyl or a group of the formula: -CO-OR<sup>5</sup> wherein R<sup>5</sup> is a hydrocarbon residue which may be substituted.
- 9. A method according to claim 1, wherein the carboxyl group which may form an amide is carboxyl or a group of the formula:

$$-CO-N \Big/ \frac{R^6}{R^7}$$

wherein  $R^6$  is a hydrogen atom or a hydrocarbon residue which may be substituted, and  $R^7$  is a hydrogen atom or a lower alkyl group or  $R^6$  and  $R^7$  may form a cyclic amino group together with the adjacent nitrogen atom.

- 10. A method according to claim 1, wherein R¹ and R² are independently a chain saturated or cyclic unsaturated hydrocarbon residue, or R¹ and R² together with the adjacent carbon atom form cyclopentyl or cyclohexyl.
- 11. A method according to claim 1, wherein R1 and R2 are independently C1-6 alkyl group.
  - 12. A method according to claim 1, wherein R1 and R2 are methyl.
  - 13. A method according to claim 1, wherein R3 is a hydrogen atom or an acyl group.
- 14. A method according to claim 13, wherein the acyl group is  $C_{1-6}$  alkyl carbonyl or  $C_{6-10}$  aryl carbonyl.
  - 15. A method according to claim 1, wherein R3 is a hydrogen atom.
  - 16. A method according to claim 1, wherein X1 is a hydrogen atom or an acyl group.
  - 17. A method according to claim 16, wherein the acyl group is an amino acid derived acyl group.
  - 18. A method according to claim 17, wherein the amino acid is glycine, alanine, glutamic acid, leucine, isoleucine, phenylalanine, aspartic acid, cysteine, sarcosine, glutamine, asparagine or proline.
  - 19. A method according to claim 17, wherein the amino acid is glycine, aspartic acid, asparagine, glutamic acid, glutamine or phenylalanine.
  - 20. A method according to claim 17, wherein the amino acid is glutamic acid or aspartic acid.

- 21. A method according to claim 1, wherein X2 is a carboxyl group which may be esterified.
- 22. A method according to claim 1, wherein X2 is a carboxyl or carbamic acyl group.
- 23. A method according to claim 22, wherein the carbamic acyl group is carbonyl amino or a carboxyl group forming an amide with an amino acid.
- 24. A method according to claim 23, wherein the amino acid is glycine, alanine, glutamic acid, leucine, isoleucine, phenylalanine, aspartic acid, cysteine, sarcosine, glutamine, asparagine or proline.
  - 25. A method according to claim 23, wherein the amino acid is glycine, aspartic acid, asparagine, pheylalanine, glutamic acid or glutamine.
- 26. A method according to claim 1, wherein R¹ and R² are independently C₁-6 alkyl, phenyl or naphthyl, or R¹ and R² form cyclopentyl or cyclohexyl together with the adjacent carbon atom; R³ is a hydrogen atom or a C₀-10 aromatic acyl group; X¹ is a hydrogen atom or an amino acid derived acyl group in which said amino acid is selected from the group consisting of glycine, aspartic acid, phenylalanine, asparagine, glutamic acid and glutamine; X² is a carboxyl group, carbonylamino or a carboxyl group forming an amide with an amino acid residue in which said amino acid is selected from the group consisting of glycine, aspartic acid, phenylalanine, asparagine, glutamic acid and glutamine.
  - 27. A method according to claim 1, wherein the salt is a pharmaceutically acceptable salt.
  - 28. A method according to claim 1, wherein said compound (I) is N-(N-L-γ-Glutamyl-D-penicillamyl)glycine.
  - 29. A method according to claim 1, wherein said compound (I) is N-(N-L-γ-Glutamyl-L-penicillamyl)-L-valine.
    - A method according to claim 1, wherein said compound (I) is N-(N-L-γ-Glutamyl-L-penicillamyl)-L-phenylalanine.
- 30 31. A method of a compound according to claim 1, wherein said compound (I) is N-(N-L-γ-Glutamyl-L-peni-cillamyl)-L-glutamic acid.
  - 32. A method according to claim 1, wherein siad compound (I) is N-(N-L-γ-Glutamyl-D-penicillamyl)diphenyl-methylamine.
  - 33. A pharmaceutical composition for use in preparation of a medicine suitable for the therapy or prophylaxis of hypertension or angina pectoris which comprises (a) as the active ingredient, an effective amount of a compound as defined in claim 1 or a salt thereof and (b) a pharmaceutically acceptable carrier, excipient or diluent therefor.
  - 34. The use of a compound as defined in claim 1 or a salt thereof for the preparation of a medicine for the therapeutic treatment of a mammal.

### 45 Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, DK, FR, GB, GR, IT, LI, LU, NL, SE

50 1. Verbindung der Formel

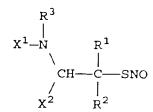
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worin

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R¹ und R² unabhängig ein Wasserstoff-Atom oder ein Kohlenwasserstoff-Rest, der substituiert sein

kann, sind;

R<sup>3</sup> ein Wasserstoff-Atom, eine Acyl-Gruppe, oder ein Kohlenwasserstoff-Rest, der substitu-

iert sein kann, ist:

X1 ein Wasserstoff-Atom, eine Acyl-Gruppe, eine niedere Alkoxy-Gruppe oder ein Kohlen-

wasserstoff-Rest, der substituiert sein kann, ist;

X<sup>2</sup> eine Acyl-Gruppe oder eine Carboxyl-Gruppe, die verestert sein oder ein Amid bilden

kann, ist;

mit der Maßgabe,

daß dann, wenn X<sup>2</sup> eine Carboxyl-Gruppe ist, X<sup>1</sup> nicht ein Wasserstoff-Atom oder eine Acetyl-Gruppe ist

daß dann, wenn R¹ und R² beide Wasserstoff-Atome sind, X¹ nicht eine Acetyl-Gruppe oder eine γ-Glutamyl-Gruppe ist, oder ein Salz derselben.

- 2. Verbindung nach Anspruch 1, worin R¹ und R² unabhängig ein Kohlenwasserstoff-Rest, der substituiert sein kann, sind oder R¹ und R² aneinander gebunden sein können und dann einen Ring der Formel -(CH<sub>2</sub>)<sub>n</sub>- bilden, worin n eine ganze Zahl von 2 bis 6 ist.
- 3. Verbindung nach Anspruch 1, worin X1 ein von einer Aminosäure abgeleitetes Acyl ist.
  - 4. Verbindung nach Anspruch 1, worin

R¹ und R² unabhängig ein Kohlenwasserstoff-Rest, der substituiert sein kann, sind;

R³ ein Wasserstoff-Atom, eine Acyl-Gruppe, oder ein Kohlenwasserstoff-Rest, der substitu-

iert sein kann, ist;

X1 ein von einer Aminosäure abgeleitetes Acyl ist;

X<sup>2</sup> eine Acyl-Gruppe oder eine Carboxyl-Gruppe, die verestert sein oder ein Amid bilden

kann, ist.

- Verbindung nach Anspruch 1, worin der Kohlenwasserstoff-Rest, der durch R¹, R², R³ oder X¹ dargestellt wird, ein kettengesättigter, kettenungesättigter, cyclisch-gesättigter oder cyclisch-ungesättigter Kohlenwasserstoff-Rest ist, der jeweils durch eine bis drei Gruppen substituiert sein kann, die aus der aus einem Halogen-Atom, Nitro, Nitril, Hydroxy, Carboxyl, C¹,-4-Alkoxy, C¹,-4-Alkylthio, Amino, Mono- oder Di-C¹,-4-Alkylamino, Mono- oder Di- aralkylamino, Mono- oder Dipyridylamino, C¹,-4-Alkoxycarbonyl, Cyclo-C₃,-6-alkylcarbonyl, Carbamoyl, Mono- oder Di-C¹,-4-alkylcarbamoyl und Phenyl, Phenoxy, Benzoyl, Phenoxycarbonyl, Phenyl-C¹,-4-alkylcarbamoyl oder der Phenylcarbamoyl-Gruppe bestehenden Klasse ausgewählt sein können, wobei jede der genannten Phenyl-Gruppen durch 1 bis 4 Gruppen substituiert sein kann, die aus der aus C¹,-4-Alkyl, einem Halogen-Atom, Hydroxyl, Benzyloxy, Amino, Mono- oder Di-C¹,-4-alkylamino, Nitro und C¹,-4-Alkoxycarbonyl bestehenden Klasse ausgewählt sein können.
  - 6. Verbindung nach Anspruch 1, worin die Acyl-Gruppe, die durch R³, X¹ oder X² dargestellt wird, eine Carbonsäure-, Carbaminsäure-, Sulfonsäure- oder Oxycarbonsäure-Acyl-Gruppe ist, die jeweils durch eine bis drei Gruppen substituiert sein kann, die aus der aus einem Halogen-Atom, Nitro, Nitril, Hydroxy, Carboxyl, C₁-₄-Alkoxy, C₁-₄-Alkylthio, Amino, Mono- oder Di-C₁-₄-alkylamino, Mono- oder Diaralkylamino, Mono- oder Dipyridylcarbonylamino, C₁-₆-Alkylcarbonyl, C₁-₄-Alkoxycarbonyl, Cyclo-C₃-₆-alkylcarbonyl, Carbamoyl, Mono- oder Di-C₁-₄-alkylcarbamoyl und Phenyl, Phenoxy, Benzoyl, Phenoxycarbonyl, Phenyl-C₁-₄-alkylcarbamoyl oder der Phenylcarbamoyl-Gruppe bestehenden Klasse ausgewählt sein können, wobei jede der genannten Phenyl-Gruppen durch 1 bis 4 Gruppen substituiert sein kann, die aus

der aus C<sub>1-4</sub>-Alkyl, einem Halogen-Atom, Hydroxyl, Benzyloxy, Amino, Mono- oder Di-C<sub>1-4</sub>-alkylamino, Nitro und C<sub>1-4</sub>-Alkoxycarbonyl bestehenden Klasse ausgewählt sein können.

- 5 7. Verbindung nach Anspruch 1, worin die niedere Alkoxy-Gruppe eine C<sub>1-8</sub>-Alkoxy-Gruppe ist.
  - 8. Verbindung nach Anspruch 1, worin die Carboxyl-Gruppe, die verestert sein kann, Carboxyl oder eine Gruppe der Formel -CO-OR<sup>5</sup> ist, worin R<sup>5</sup> ein Kohlenwasserstoff-Rest ist, der substituiert sein kann.
- Verbindung nach Anspruch 1, worin die Carboxyl-Gruppe, die ein Amid bilden kann, Carboxyl oder eine Gruppe der Formel

-CO-N R

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 $R^6$ 

ein Wasserstoff-Atom oder ein Kohlenwasserstoff-Rest, der substituiert sein kann, ist und

 $R^7$ 

ein Wasserstoff-Atom oder eine niedere Alkyl-Gruppe ist oder

R<sup>6</sup> und R<sup>7</sup>

zusammen mit dem benachbarten Stickstoff-Atom eine cyclische Amino-Gruppe bilden

können.

- 10. Verbindung nach Anspruch 1, worin R¹ und R² unabhängig ein kettengesättigter oder ein cyclisch-ungesättigter Kohlenwasserstoff-Rest sind oder R¹und R² zusammen mit dem benachbarten Kohlenstoff-Atom Cyclopentyl oder Cyclohexyl bilden.
  - 11. Verbindung nach Anspruch 1, worin R<sup>1</sup> und R<sup>2</sup> unabhängig eine C<sub>1-8</sub>-Alkyl-Gruppe sind.
  - 12. Verbindung nach Anspruch 1, worin R1 und R2 Methyl sind.
  - 13. Verbindung nach Anspruch 1, worin R3 ein Wasserstoff-Atom oder eine Acyl-Gruppe ist.
- 35 14. Verbindung nach Anspruch 13, worin die Acyl-Gruppe C<sub>1-6</sub>-Alkylcarbonyl- oder C<sub>6-10</sub>Arylcarbonyl ist.
  - 15. Verbindung nach Anspruch 1, worin R³ ein Wasserstoff-Atom ist.
  - 16. Verbindung nach Anspruch 1, worin X1 ein Wasserstoff-Atom oder eine Acyl-Gruppe ist.
- 40 17. Verbindung nach Anspruch 16, worin die Acyl-Gruppe eine von einer Aminosäure abgeleitete Acyl-Gruppe ist.
  - 18. Verbindung nach Anspruch 17, worin die Aminosäure Glycin, Alanin, Glutaminsäure, Leucin, Isoleucin, Phenylalanin, Asparaginsäure, Cystein, Sarcosin, Glutamin, Asparagin oder Prolin ist.
  - Verbindung nach Anspruch 17, worin die Aminosäure Glycin, Asparaginsäure, Asparagin, Glutaminsäure, Glutamin oder Phenylalanin ist.
  - 20. Verbindung nach Anspruch 17, worin die Aminosäure Glutaminsäure oder Asparaginsäure ist.
  - 21. Verbindung nach Anspruch 1, worin X<sup>2</sup> eine Carboxyl-Gruppe ist, die verestert sein kann.
  - 22. Verbindung nach Anspruch 1, worin X<sup>2</sup> eine Carboxyl- oder eine Carbaminsäure-Acyl-Gruppe ist.
- 23. Verbindung nach Anspruch 22, worin die Carbaminsäure-Acyl-Gruppe Carbonylamino oder eine mit einer Aminosäure ein Amid bildende Carboxyl-Gruppe ist.
  - 24. Verbindung nach Anspruch 23, worin die Aminosäure Glycin, Alanin, Glutaminsäure, Leucin, Isoleucin, Phenylalanin, Asparaginsäure, Cystein, Sarcosin, Glutamin, Asparagin oder Prolin ist.

- 25. Verbindung nach Anspruch 23, worin die Aminosäure Glycin, Asparaginsäure, Asparagin, Phenylalanin, Glutaminsäure oder Glutamin ist.
- 26. Verbindung nach Anspruch 1, worin

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 $X^2$ 

R¹ und R² unabhängig C<sub>1-6</sub>-Alkyl, Phenyl oder Naphthyl sind oder R¹ und R² zusammen mit dem benachbarten Kohlenstoff-Atom Cyclopentyl oder Cyclohexyl bilden;

R<sup>3</sup> ein Wasserstoff-Atom oder eine aromatische C<sub>6-10</sub>-Acyl-Gruppe ist;

X1 ein Wasserstoff-Atom oder eine von einer Aminosäure abgeleitete Acyl-Gruppe ist, wobei die Aminosäure aus der aus Glycin, Asparaginsäure, Phenylalanin, Asparagin, Glutamin-

säure und Glutamin bestehenden Gruppe ausgewählt ist;

eine Carboxyl-Gruppe, Carbonylamino oder eine mit einem Aminosäure-Rest ein Amid bildende Carboxyl-Gruppe ist, wobei die Aminosäure aus der aus Glycin, Asparaginsäure, Phenylalanin, Asparagin, Glutaminsäure und Glutamin bestehenden Gruppe ausgewählt

ist.

- 27. Verbindung nach Anspruch 1, worin das Salz ein pharmazeutisch unbedenkliches Salz ist.
- 28. Verbindung nach Anspruch 1, die N-(N-L-γ-Glutamyl-D-penicillamyl)glycin ist.
- 29. Verbindung nach Anspruch 1, die N-(N-L-γ-Glutamyl-L-penicillamyt)-L-valin ist.
  - 30. Verbindung nach Anspruch 1, die N-(N-L-γ-Glutamyl-L-penicillamyl)-L-phenylalanin ist.
  - 31. Verbindung nach Anspruch 1, die N-(N-L-y-Glutamyl-L-penicillamyl)-L-glutaminsäure ist.
  - 32. Verbindung nach Anspruch 1, die N-(N-L-y-Glutamyl-D-penicillamyl)diphenylmethylamin ist
  - 33. Pharmazeutische Zusammensetzung, die für die Therapie oder Prophylaxe von Bluthochdruck oder Angina pectoris geeignet ist, umfassend
    - (a) als Wirkstoff eine wirksame Menge einer Verbindung nach Anspruch 1 oder eines Salzes derselben und
    - (b) ein pharmazeutisch unbedenkliches Trägermaterial, Streckmittel oder Verdünnungsmittel für diese.
  - 34. Verwendung einer Verbindung nach Anspruch 1 oder eines Salzes derselben zu Herstellung eines Medikaments zur therapeutischen Behandlung eines Säugers.
  - 35. Verfahren zur Herstellung einer Verbindung der Formel (I)

 $X^{1}$   $X^{1}$   $X^{1}$   $X^{1}$   $X^{2}$   worin

R¹ und R² unabhängig ein Wasserstoff-Atom oder ein Kohlenwasserstoff-Rest, der substituiert sein

kann, sind;

R<sup>3</sup> ein Wasserstoff-Atom, eine Acyl-Gruppe, oder ein Kohlenwasserstoff-Rest, der substituiert sein kann, ist;

X<sup>1</sup> ein Wasserstoff-Atom, eine Acyl-Gruppe, eine niedere Alkoxy-Gruppe oder ein Kohlenwasserstoff-Rest, der substituiert sein kann, ist;

X<sup>2</sup> eine Acyl-Gruppe oder eine Carboxyl-Gruppe, die verestert sein oder ein Amid bilden

kann, ist;

mit der Maßgabe,

daß dann, wenn  $X^2$  eine Carboxyl-Gruppe ist,  $X^1$  nicht ein Wasserstoff-Atom oder eine Acetyl-Gruppe ist und

daß dann, wenn  $R^1$  und  $R^2$  beide Wasserstoff-Atome sind,  $X^1$  nicht eine Acetyl-Gruppe oder eine  $\gamma$ -Glutamyl-Gruppe ist, oder eines Salzes derselben, umfassend

(a) die Durchführung einer Nitrosierungs-Reaktion mit einer Verbindung der Formel (II)

worin

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R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, X<sup>1</sup> und X<sup>2</sup> die gleichen sind, wie sie oben beschrieben sind, und gewünschtenfalls (b) die Überführung des durch das obige Verfahren (a) erhaltenen Produkts in ein Salz desselben.

## Patentansprüche für folgenden Vertragsstaat : ES

## 1. Verfahren zur Herstellung einer Verbindung der Formel (I)

$$\begin{array}{ccc}
R^{3} \\
| & & \\
X^{1}-N & R^{1} \\
& & | & \\
CH--C--SNC \\
/ & | & \\
X^{2} & R^{2}
\end{array}$$

worin

R¹ und R² unabhängig ein Wasserstoff-Atom oder ein Kohlenwasserstoff-Rest, der substituiert sein

kann, sind;

R<sup>3</sup> ein Wasserstoff-Atom, eine Acyl-Gruppe, oder ein Kohlenwasserstoff-Rest, der substitu-

iert sein kann, ist;

X1 ein Wasserstoff-Atom, eine Acyl-Gruppe, eine niedere Alkoxy-Gruppe oder ein Kohlen-

wasserstoff-Rest, der substituiert sein kann, ist;

40 X<sup>2</sup> eine Acyl-Gruppe oder eine Carboxyl-Gruppe, die verestert sein oder ein Amid bilden

kann, ist;

mit der Maßgabe,

daß dann, wenn X² eine Carboxyl-Gruppe ist, X¹ nicht ein Wasserstoff-Atom oder eine Acetyl-Gruppe ist

daß dann, wenn R¹ und R² beide Wasserstoff-Atome sind, X¹ nicht eine Acetyl-Gruppe oder eine γ-Glut-

amyl-Gruppe ist, oder eines Salzes derselben,

umfassend

(a) die Durchführung einer Nitrosierungs-Reaktion mit einer Verbindung der Formel (II)

worin

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R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, X<sup>1</sup> und X<sup>2</sup> die gleichen sind, wie sie oben beschrieben sind, und gewünschtenfalls (b) die Überführung des durch das obige Verfahren (a) erhaltenen Produkts in ein Salz desselben.

- Verfahren nach Anspruch 1, wonn R1 und R2 unabhängig ein Kohlenwasserstoff-Rest, der substituiert sein kann, sind oder R1 und R2 aneinander gebunden sein können und dann einen Ring der Formel -(CH<sub>2</sub>)<sub>n</sub>- bilden, worin n eine ganze Zahl von 2 bis 6 ist.
- Verfahren nach Anspruch 1, worin X1 ein von einer Aminosäure abgeleitetes Acyl ist. 10
  - Verfahren nach Anspruch 1, worin

R1 und R2 unabhängig ein Kohlenwasserstoff-Rest, der substituiert sein kann, sind;

 $R^3$ ein Wasserstoff-Atom, eine Acyl-Gruppe, oder ein Kohlenwasserstoff-Rest, der substitu-

iert sein kann, ist;

Χ¹ ein von einer Aminosäure abgeleitetes Acyl ist;

 $X^2$ eine Acyl-Gruppe oder eine Carboxyl-Gruppe, die verestert sein oder ein Amid bilden kann, ist.

- Verfahren nach Anspruch 1, worin der Kohlenwasserstoff-Rest, der durch R1, R2, R3 oder X1 dargestellt 20 wird, ein kettengesättigter, kettenungesättigter, cyclisch-gesättigter oder cyclisch-ungesättigter Kohlenwasserstoff-Rest ist, der jeweils durch eine bis drei Gruppen substituiert sein kann, die aus der aus einem Halogen-Atom, Nitro, Nitril, Hydroxy, Carboxyl, C<sub>1-4</sub>-Alkoxy, C<sub>1-4</sub>-Alkylthio, Amino, Mono- oder Di-C<sub>1-4</sub>alkylamino, Mono- oder Di-aralkylamino, Mono- oder Dipyridylamino, C1-4-Alkoxycarbonyl, Cyclo-C3-6alkylcarbonyl, Carbamoyl, Mono- oder Di-C1-4-alkylcarbamoyl und Phenyl, Phenoxy, Benzoyl, 25 Phenoxycarbonyl, Phenyl-C<sub>1-4</sub>-alkylcarbamoyl oder der Phenylcarbamoyl-Gruppe bestehenden Klasse ausgewählt sein können, wobei jede der genannten Phenyl-Gruppen durch 1 bis 4 Gruppen substituiert sein kann, die aus der aus C<sub>1-4</sub>-Alkyl, einem Halogen-Atom, Hydroxyl, Benzyloxy, Amino, Mono- oder Di-C<sub>1-4</sub>-alkylamino, Nitro und C<sub>1-4</sub>-Alkoxycarbonyl bestehenden Klasse ausgewählt sein können.
- 30 Verfahren nach Anspruch 1, worin die Acyl-Gruppe, die durch R3, X1 oder X2 dargestellt wird, eine Carbonsäure-, Carbaminsäure-, Sulfonsäure- oder Oxycarbonsäure-Acyl-Gruppe ist, die jeweils durch eine bis drei Gruppen substituiert sein kann, die aus der aus einem Halogen-Atom, Nitro, Nitril, Hydroxy, Carboxyl, C<sub>1-4</sub>-Alkoxy, C<sub>1-4</sub>-Alkylthio, Amino, Mono- oder Di-C<sub>1-4</sub>-alkylamino, Mono- oder Diaralkylamino,  $\label{eq:control_control_control} Mono-\ oder\ Dipyridylcarbonylamino,\ C_{1-6}-Alkylcarbonyl,\ C_{1-4}-Alkoxycarbonyl,\ Cyclo-C_{3-6}-alkylcarbonyl,\ C_{1-6}-Alkylcarbonyl,\ C_{1-6}-Alkylcarbony$ 35 Carbamoyl, Mono- oder Di-C1-4-alkylcarbamoyl und Phenyl, Phenoxy, Benzoyl, Phenoxycarbonyl, Phenyl-C<sub>1-4</sub>-alkylcarbamoyl oder der Phenylcarbamoyl-Gruppe bestehenden Klasse ausgewählt sein konnen, wobei jede der genannten Phenyl-Gruppen durch 1 bis 4 Gruppen substituiert sein kann, die aus der aus C1-4-Alkyl, einem Halogen-Atom, Hydroxyl, Benzyloxy, Amino, Mono- oder Di-C1-4-alkylamino, 40 Nitro und C<sub>1-4</sub>-Alkoxycarbonyl bestehenden Klasse ausgewählt sein können.
  - 7. Verfahren nach Anspruch 1, worin die niedere Alkoxy-Gruppe eine C<sub>1-6</sub>-Alkoxy-Gruppe ist.
- 8. Verfahren nach Anspruch 1, worin die Carboxyl-Gruppe, die verestert sein kann, Carboxyl oder eine Gruppe der Formel -CO-OR5 ist, worin R5 ein Kohlenwasserstoff-Rest ist, der substituiert sein kann. 45
  - Verfahren nach Anspruch 1, worin die Carboxyl-Gruppe, die ein Amid bilden kann, Carboxyl oder eine Gruppe der Formel

-CO-N

ist, worin

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 $R^6$ ein Wasserstoff-Atom oder ein Kohlenwasserstoff-Rest, der substituiert sein kann, ist und ein Wasserstoff-Atom oder eine niedere Alkyl-Gruppe ist oder  $R^7$ 

- R<sup>6</sup> und R<sup>7</sup> zusammen mit dem benachbarten Stickstoff-Atom eine cyclische Amino-Gruppe bilden können.
- 10. Verfahren nach Anspruch 1, worin R¹ und R² unabhängig ein kettengesättigter oder ein cyclisch-ungesättigter Kohlenwasserstoff-Rest sind oder R¹und R² zusammen mit dem benachbarten Kohlenstoff-Atom Cyclopentyl oder Cyclohexyl bilden.
  - 11. Verfahren nach Anspruch 1, worin R1 und R2 unabhängig eine C1-6-Alkyl-Gruppe sind.
- 10 12. Verfahren nach Anspruch 1, worin R<sup>1</sup> und R<sup>2</sup> Methyl sind.

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- 13. Verfahren nach Anspruch 1, worin R<sup>3</sup> ein Wasserstoff-Atom oder eine Acyl-Gruppe'ist.
- 14. Verfahren nach Anspruch 13, worin die Acyl-Gruppe C<sub>1-8</sub>-Alkylcarbonyl- oder C<sub>8-10</sub>Arylcarbonyl ist.
- 15. Verfahren nach Anspruch 1, worin R3 ein Wasserstoff-Atom ist.
- 16. Verfahren nach Anspruch 1, worin X1 ein Wasserstoff-Atom oder eine Acyl-Gruppe ist.
- Verfahren nach Anspruch 16, worin die Acyl-Gruppe eine von einer Aminosäure abgeleitete Acyl-Gruppe ist.
  - **18.** Verfahren nach Anspruch 17, worin die Aminosäure Glycin, Alanin, Glutaminsäure, Leucin, Isoleucin, Phenylalanin, Asparaginsäure, Cystein, Sarcosin, Glutamin, Asparagin oder Prolin ist.
- 19. Verfahren nach Anspruch 17, worin die Aminosäure Glycin, Asparaginsäure, Asparagin, Glutaminsäure, Glutamin oder Phenylalanin ist.
  - 20. Verfahren nach Anspruch 17, worin die Aminosäure Glutaminsäure oder Asparaginsäure ist.
- 30 21. Verfahren nach Anspruch 1, worin X<sup>2</sup> eine Carboxyl-Gruppe ist, die verestert sein kann.
  - 22. Verfahren nach Anspruch 1, worin X² eine Carboxyl- oder eine Carbaminsäure-Acyl-Gruppe ist.
- 23. Verfahren nach Anspruch 22, worin die Carbaminsäure-Acyl-Gruppe Carbonylamino oder eine mit einer Aminosäure ein Amid bildende Carboxyl-Gruppe ist.
  - 24. Verfahren nach Anspruch 23, worin die Aminosäure Glycin, Alanin, Glutaminsäure, Leucin, Isoleucin, Phenylalanin, Asparaginsäure, Cystein, Sarcosin, Glutamin, Asparagin oder Prolin ist.
- 25. Verfahren nach Anspruch 23, worin die Aminosäure Glycin, Asparaginsäure, Asparagin, Phenylalanin,
  Glutaminsäure oder Glutamin ist.
  - 26. Verfahren nach Anspruch 1, worin
    - R<sup>1</sup> und R<sup>2</sup> unabhängig C<sub>1-8</sub>-Alkyl, Phenyl oder Naphthyl sind oder R<sup>1</sup> und R<sup>2</sup> zusammen mit dem benachbarten Kohlenstoff-Atom Cyclopentyl oder Cyclohexyl bilden;
    - R<sup>3</sup> ein Wasserstoff-Atom oder eine aromatische C<sub>8-10</sub>-Acyl-Gruppe ist;
    - X1 ein Wasserstoff-Atom oder eine von einer Aminosäure abgeleitete Acyl-Gruppe ist, wobei die Aminosäure aus der aus Glycin, Asparaginsäure, Phenylalanin, Asparagin, Glutaminsäure und Glutamin bestehenden Gruppe ausgewählt ist;
    - X<sup>2</sup> eine Carboxyl-Gruppe, Carbonylamino oder eine mit einem Aminosäure-Rest ein Amid bildende Carboxyl-Gruppe ist, wobei die Aminosäure aus der aus Glycin, Asparaginsäure, Phenylalanin, Asparagin, Glutaminsäure und Glutamin bestehenden Gruppe ausgewählt ist
  - 27. Verfahren nach Anspruch 1, worin das Salz ein pharmazeutisch unbedenkliches Salz ist
  - 28. Verfahren nach Anspruch 1, die N-(N-L-y-Glutamyl-D-penicillamyl)glycin ist.
  - 29. Verfahren nach Anspruch 1, die N-(N-L-γ-Glutamyl-L-penicillamyl)-L-valin ist.

- 30. Verfahren nach Anspruch 1, die N-(N-L-y-Glutamyl-L-penicillamyl)-L-phenylalanin ist.
- 31. Verfahren nach Anspruch 1, die N-(N-L-γ-Glutamyl-L-penicillamyl)-L-glutaminsäure ist.
- 32. Verfahren nach Anspruch 1, die N-(N-L-y-Glutamyl-D-penicillamyl)diphenylmethylamin ist.
- 33. Pharmazeutische Zusammensetzung, die für die Therapie oder Prophylaxe von Bluthochdruck oder Angina pectoris geeignet ist, umfassend
  - (a) als Wirkstoff eine wirksame Menge einer Verbindung, wie sie in Anspruch 1 definiert ist, oder eines Salzes derselben und
  - (b) ein pharmazeutisch unbedenkliches Trägermaterial, Streckmittel oder Verdünnungsmittel für diese.
- 34. Verwendung einer Verbindung, wie sie in Anspruch 1 definiert ist, oder eines Salzes derselben zu Herstellung eines Medikaments zur therapeutischen Behandlung eines Säugers.

#### Revendications

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- Revendications pour les Etats contractants suivants : AT, BE, CH, DE, DK, FR, GB, GR, IT, LI, LU, NL, SE
  - 1. Composé de formule:

$$X_{1} - \frac{X_{1}}{1} > CII - \frac{1}{C} - 240$$

dans laquelle  $R^1$  et  $R^2$  sont, indépendamment l'un de l'autre, un atome d'hydrogène ou un radical hydrocarboné qui peut être substitué;  $R^3$  est un atome d'hydrogène, un groupe acyle ou un radical hydrocarboné qui peut être substitué;  $X^1$  est un atome d'hydrogène, un groupe acyle, un groupe alcoxy inférieur ou un radical hydrocarboné qui peut être substitué;  $X^2$  est un groupe acyle ou un groupe carboxylique qui peut être estérifié ou qui peut former un amide; avec la condition que  $X^1$  n'est pas un atome d'hydrogène ou le groupe acétyle lorsque  $X^2$  est un groupe carboxylique et que  $X^1$  n'est pas un groupe acétyle ou un groupe  $\gamma$ -glutamyle lorsque  $R^1$  et  $R^2$  sont tous deux des atomes d'hydrogène, ou un sel de celui-ci.

- 2. Composé selon la revendication 1, dans lequel R¹ et R² sont, indépendamment l'un de l'autre, un radical hydrocarboné qui peut être substitué ou R¹ et R² peuvent être liés l'un à l'autre pour former un cycle de formule: -(CH<sub>2</sub>)<sub>n</sub>- dans laquelle n est un nombre entier de 2 à 6.
  - 3. Composé selon la revendication 1, dans lequel X1 est un acyle dérivé d'un acide aminé.
- 45 4. Composé selon la revendication 1, dans lequel R¹ et R² sont, indépendamment l'un de l'autre, un radical hydrocarboné qui peut être substitué; R³ est un atome d'hydrogène, un groupe acyle ou un radical hydrocarboné qui peut être substitué; X¹ est un acyle dérivé d'un acide aminé; X² est un groupe acyle ou un groupe carboxylique qui peut être estérifié ou qui peut former un amide.
- 5. Composé selon la revendication 1, dans lequel le radical hydrocarboné représenté par R¹, R², R³ ou X¹ est un radical hydrocarboné à chaîne saturée, à chaîne insaturée, un radical hydrocarboné cyclique saturé ou cyclique insaturé, dont chacun peut être substitué par un à trois groupes choisis dans le groupe consistant en un atome d'halogène, un groupe nitro, nitrile, hydroxyle, carboxylique, alcoxy en C₁-₄, alcoylthio en C₁-₄, amino, mono ou di(alcoyle en C₁-₄)amino, mono ou di-aralcolyamino, mono ou di-pyridylamino, alcoxy en C₁-₄-carbonyle, cycloalcoyle en C₃-₅-carbonyle, carbamoyle, mono ou di(alcoyle en C₁-₄)carbamoyle et un groupe phényle, phénoxy, benzoyle, phénoxycarbonyle, phénylalcoyle en C₁-₄-carbamoyle ou phénylcarbamoyle, dans lesquels chacun desdits groupes phényle peut être substitué par 1 à 4 groupes choisis dans le groupe consistant en un alcoyle en C₁-₄, un atome d'halogène, un groupe hydroxyle, ben-

zyloxy, amino, mono ou di(alcoyle en  $C_{1-4}$ )amino, nitro et alcoxy en  $C_{1-4}$ -carbonyle.

- 6. Composé selon la revendication 1, dans lequel le groupe acyle représenté par R³, X¹ ou X² est un groupe acyle carboxylique, carbamique, sulfonique ou oxycarboxylique dont chacun peut être substitué par 1 à 3 groupes choisis dans le groupe consistant en un atome d'halogène, un groupe nitro, nitrile, hydroxyle, carboxylique, alcoxy en C₁-₄, alcoylthio en C₁-₄, amino, mono ou di(alcoyle en C₁-₄)amino, mono ou di-aralcoylamino, mono ou di-pyridylcarbonylamino, alcoyle en C₁-₄-carbonyle, alcoxy en C₁-₄-carbonyle, cycloalcoyle en C₃-₆-carbonyle, carbamoyle, mono ou di(alcoyle en C₁-₄)-carbamoyle et un groupe phényle, phénoxy, benzoyle, phénoxycarbonyle, phényl-alcoyle en C₁-₄-carbamoyle ou phénylcarbamoyle dans lesquels chacun desdits groupes phényle peut être substitué par 1 à 4 groupes choisis dans le groupe consistant en un alcoyle en C₁-₄, un atome d'halogène, un groupe hydroxyle, benzyloxy, amino, mono ou di(alcoyle en C₁-₄)amino, nitro et alcoxy en C₁-₄-carbonyle.
- 7. Composé selon la revendication 1, dans lequel le groupe alcoxy inférieur est un groupe alcoxy en C<sub>1-6</sub>.
  - 8. Composé selon la revendication 1, dans lequel le groupe carboxylique qui peut être estérifié est un carboxyle ou un groupe de formule: -CO-OR<sup>5</sup>, dans laquelle R<sup>5</sup> est un radical hydrocarboné qui peut être substitué.
  - 9. Composé selon la revendication 1, dans lequel le groupe carboxylique qui peut former un amide est un carboxyle ou un groupe de formule:

$$-CO-N \Big< \frac{R^6}{R^7}$$

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- dans laquelle R<sup>6</sup> est un atome d'hydrogène ou un radical hydrocarboné qui peut être substitué et R<sup>7</sup> est un atome d'hydrogène ou un groupe alcoyle inférieur ou R<sup>6</sup> et R<sup>7</sup> forment ensemble avec l'atome d'azote adjacent un groupe amino cyclique.
- 10. Composé selon la revendication 1, dans lequel R¹ et R² sont, indépendamment l'un de l'autre, un radical hydrocarboné à chaîne saturée ou cyclique insaturée ou R¹ et R² forment ensemble avec l'atome de carbone adjacent un groupe cyclopentyle ou cyclohexyle.
  - 11. Composé selon la revendication 1, dans lequel R¹ et R² sont, indépendamment l'un de l'autre, un groupe alcoyle en C<sub>1-6</sub>.
- 12. Composé selon la revendication 1, dans lequel R¹ et R² sont un méthyle.
  - 13. Composé selon la revendication 1, dans lequel R<sup>3</sup> est un atome d'hydrogène ou un groupe acyle.
- 14. Composé selon la revendication 13, dans lequel le groupe acyle est un alcoyle en C<sub>1-6</sub>-carbonyle ou un aryle en C<sub>8-10</sub>-carbonyle.
  - 15. Composé selon la revendication 1, dans lequel R<sup>3</sup> est un atome d'hydrogène.
  - 16. Composé selon la revendication 1, dans lequel X1 est un atome d'hydrogène ou un groupe acyle.
- Composé selon la revendication 16, dans lequel le groupe acyle est un groupe acyle dérivé d'un acide aminé.
  - 18. Composé selon la revendication 17, dans lequel l'acide aminé est la glycine, l'alanine, l'acide glutamique, la leucine, l'isoleucine, la phénylalanine, l'acide aspartique, la cystéine, la sarcosine, la glutamine, l'asparagine ou la proline.
  - 19. Composé selon la revendication 17, dans lequel l'acide aminé est la glycine, l'acide aspartique, l'asparagine, l'acide glutamique, la glutamine ou la phénylalanine.

- 20. Composé selon la revendication 17, dans lequel l'acide aminé est l'acide glutamique ou l'acide aspartique.
- 21. Composé selon la revendication 1, dans lequel X<sup>2</sup> est un groupe carboxylique qui peut être estérifié.
- 22. Composé selon la revendication 1, dans lequel X<sup>2</sup> est un groupe acyle carboxylique ou carbamique.
- 23. Composé selon la revendication 22, dans lequel le groupe acyle carbamique est un groupe aminocarbonyle ou un groupe carboxylique formant un amide avec un acide aminé.
- 24. Composé selon la revendication 23, dans lequel l'acide aminé est la glycine, l'alanine, l'acide glutamique, la leucine, l'isoleucine, la phénylalanine, l'acide aspartique, la cystéine, la sarcosine, la glutamine, l'asparagine ou la proline.
  - 25. Composé selon la revendication 23, dans lequel l'acide aminé est la glycine, l'acide aspartique, l'asparagine, la phénylalanine, l'acide glutamique ou la glutamine.
    - 26. Composé selon la revendication 1, dans lequel R¹ et R² sont, indépendamment l'un de l'autre, un groupe alcoyle en C₁-6, phényle ou náphtyle ou R¹ et R² forment ensemble avec l'atome de carbone adjacent un groupe cyclopentyle ou cyclohexyle; R³ est un atome d'hydrogène ou un groupe acyle aromatique en C₅-10; X¹ est un atome d'hydrogène ou un groupe acyle dérivé d'un acide aminé dans lequel ledit acide aminé est choisi dans le groupe consistant en la glycine, l'acide aspartique, la phénylalanine, l'asparagine, l'acide glutamique et la glutamine; X² est un groupe carboxylique, aminocarbonyle ou un groupe carboxylique formant un amide avec un radical d'acide aminé dans lequel ledit acide aminé est choisi dans le groupe consistant en la glycine, l'acide aspartique, la phénylalanine, l'asparagine, l'acide glutamique et la glutamine.
    - 27. Composé selon la revendication 1, dans lequel le sel est un sel pharmaceutiquement acceptable.
    - 28. Composé selon la revendication 1, qui est la N-(N-L-γ-glutamyl-D-pénicillamyl)glycine.
    - 29. Composé selon la revendication 1, qui est la N-(N-L-γ-glutamyl-L-pénicillamyl)-L-valine.
    - 30. Composé selon la revendication 1, qui est la N-(N-L-γ-glutamyl-L-pénicillamyl)-phénylalanine.
    - 31. Composé selon la revendication 1, qui est l'acide N-(N-L-y-glutamyl-L-pénicillamyl)-L-glutamique.
    - 32. Composé selon la revendication 1, qui est la N-(N-L-γ-glutamyl-D-pénicillamyl)diphénylméthylamine.
  - 33. Composition pharmaceutique propre au traitement curatif ou prophylactique de l'hypertension ou de l'angine de poitrine, qui comprend (a) comme substance active, une quantité efficace d'un composé selon la revendication 1 ou d'un sel de celui-ci et (b) une matière de support, un excipient ou un diluant pharmaceutiquement acceptable pour ce composé.
    - 34. Utilisation d'un composé selon la revendication 1 ou d'un sel de celui-ci pour la préparation d'un médicament pour le traitement thérapeutique d'un mammifère.
  - 35. Procédé de préparation d'un composé de formule (I):

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$$X' - \frac{R^2}{N}$$
 CH  $-\frac{C}{C}$  SNO

dans laquelle R¹ et R² sont, indépendamment l'un de l'autre, un atome d'hydrogène ou un radical hydrocarboné qui peut être substitué; R³ est un atome d'hydrogène, un groupe acyle ou un radical hydrocarboné qui peut être substitué; X¹ est un atome d'hydrogène, un groupe acyle, un groupe alcoxy inférieur ou un radical hydrocarboné qui peut être substitué; X² est un groupe acyle ou un groupe carboxylique qui peut être estérifié ou qui peut former un amide; avec la condition que X¹ n'est pas un atome d'hydrogène ou le groupe acétyle lorsque  $X^2$  est un groupe carboxylique et que  $X^1$  n'est pas un groupe acétyle ou un groupe  $\gamma$ -glutamyle lorsque  $R^1$  et  $R^2$  sont tous deux des atomes d'hydrogène, ou d'un sel de celui-ci, selon lequel

(a) on soumet un composé de formule (II):

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$$X_{1} - \frac{1}{N} > CII - \frac{1}{N} = SII$$

dans laquelle R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, X<sup>1</sup> et X<sup>2</sup> sont tels que défini ci-dessus, à une réaction de nitrosation et, si désiré, (b) on transforme le produit obtenu par le procédé (a) ci-dessus en un sel de celui-ci.

# Revendications pour l'Etat contractant suivant : ES

1. Procédé de préparation d'un composé de formule (I):

$$X_1 - \frac{1}{N}$$
 > CII -  $\frac{1}{N}$  = SHO

dans laquelle  $R^1$  et  $R^2$  sont, indépendamment l'un de l'autre, un atome d'hydrogène ou un radical hydrocarboné qui peut être substitué;  $R^3$  est un atome d'hydrogène, un groupe acyle ou un radical hydrocarboné qui peut être substitué;  $X^1$  est un atome d'hydrogène, un groupe acyle, un groupe alcoxy inférieur ou un radical hydrocarboné qui peut être substitué;  $X^2$  est un groupe acyle ou un groupe carboxylique qui peut être estérifié ou qui peut former un amide; avec la condition que  $X^1$  n'est pas un atome d'hydrogène ou le groupe acétyle lorsque  $X^2$  est un groupe carboxylique et que  $X^1$  n'est pas un groupe acétyle ou un groupe  $Y^2$  est un groupe carboxylique et que  $Y^2$  peut qui peut de celui-ci, selon lequel

(a) on soumet un composé de formule (II):

$$\frac{X_{i}}{N} > CH - \frac{K_{i}}{C} = SH$$

dans laquelle R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, X<sup>1</sup> et X<sup>2</sup> sont tels que défini ci-dessus, à une réaction de nitrosation et, si désiré, (b) on transforme le produit obtenu par le procédé (a) ci-dessus en un sel de celui-ci.

- 2. Procédé selon la revendication 1, dans lequel R¹ et R² sont, indépendamment l'un de l'autre, un radical hydrocarboné qui peut être substitué ou R¹ et R² peuvent être liés l'un à l'autre pour former un cycle de formule: -(CH<sub>2</sub>)<sub>n</sub>- dans laquelle n est un nombre entier de 2 à 6.
- 3. Procédé selon la revendication 1, dans lequel X1 est un acyle dérivé d'un acide aminé.
- 4. Procédé selon la revendication 1, dans lequel R¹ et R² sont, indépendamment l'un de l'autre, un radical hydrocarboné qui peut être substitué; R³ est un atome d'hydrogène, un groupe acyle ou un radical hydrocarboné qui peut être substitué; X¹ est un acyle dérivé d'un acide aminé; X² est un groupe acyle ou un groupe carboxylique qui peut être estérifié ou qui peut former un amide.

- 5. Procédé selon la revendication 1, dans lequel le radical hydrocarboné représenté par R¹, R², R³ ou X¹ est un radical hydrocarboné à chaîne saturée, à chaîne insaturée, un radical hydrocarboné cyclique saturé ou cyclique insaturé, dont chacun peut être substitué par un à trois groupes choisis dans le groupe consistant en un atome d'halogène, un groupe nitro, nitrile, hydroxyle, carboxylique, alcoxy en C₁₋₄, alcoylthio en C₁₋₄, amino, mono ou di(alcoyle en C₁₋₄)amino, mono ou di-aralcolyamino, mono ou di-pyridylamino, alcoxy en C₁₋₄-carbonyle, cycloalcoyle en C₃₋6-carbonyle, carbamoyle, mono ou di(alcoyle en C₁₋₄)carbamoyle et un groupe phényle, phénoxy, benzoyle, phénoxycarbonyle, phénylalcoyle en C₁₋₄-carbamoyle ou phénylcarbamoyle, dans lesquels chacun desdits groupes phényle peut être substitué par 1 à 4 groupes choisis dans le groupe consistant en un alcoyle en C₁₋₄, un atome d'halogène, un groupe hydroxyle, benzyloxy, amino, mono ou di(alcoyle en C₁₋₄)amino, nitro et alcoxy en C₁₋₄-carbonyle.
- 6. Procédé selon la revendication 1, dans lequel le groupe acyle représenté par R³, X¹ ou X² est un groupe acyle carboxylique, carbamique, sulfonique ou oxycarboxylique dont chacun peut être substitué par 1 à 3 groupes choisis dans le groupe consistant en un atome d'halogène, un groupe nitro, nitrile, hydroxyle, carboxylique, alcoxy en C₁-₄, alcoylthio en C₁-₄, amino, mono ou di(alcoyle en C₁-₄)amino, mono ou di-aralcoylamino, mono ou di-pyridylcarbonylamino, alcoyle en C₁-ሬ-carbonyle, alcoxy en C₁-₄-carbonyle, cycloalcoyle en C₃-ሬ-carbonyle, carbamoyle, mono ou di(alcoyle en C₁-₄)-carbamoyle et un groupe phényle, phénoxy, benzoyle, phénoxycarbonyle, phényl-alcoyle en C₁-₄-carbamoyle ou phénylcarbamoyle dans lesquels chacun desdits groupes phényle peut être substitué par 1 à 4 groupes choisis dans le groupe consistant en un alcoyle en C₁-₄, un atome d'halogène, un groupe hydroxyle, benzyloxy, amino, mono ou di(alcoyle en C₁-₄)amino, nitro et alcoxy en C₁-₄-carbonyle.
- 7. Procédé selon la revendication 1, dans lequel le groupe alcoxy inférieur est un groupe alcoxy en C<sub>1-8</sub>.
  - 8. Procédé selon la revendication 1, dans lequel le groupe carboxylique qui peut être estérifié est un carboxyle ou un groupe de formule: -CO-OR<sup>5</sup>, dans laquelle R<sup>5</sup> est un radical hydrocarboné qui peut être substitué.
- Procédé selon la revendication 1, dans lequel le groupe carboxylique qui peut former un amide est un carboxyle ou un groupe de formule:

$$-CO-N \left\langle \frac{R^{6}}{R^{7}} \right\rangle$$

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dans laquelle R<sup>6</sup> est un atome d'hydrogène ou un radical hydrocarboné qui peut être substitué et R<sup>7</sup> est un atome d'hydrogène ou un groupe alcoyle inférieur ou R<sup>6</sup> et R<sup>7</sup> forment ensemble avec l'atome d'azote adjacent un groupe amino cyclique.

- 10. Procédé selon la revendication 1, dans lequel R¹ et R² sont, indépendamment l'un de l'autre, un radical hydrocarboné à chaîne saturée ou cyclique insaturée ou R¹ et R² forment ensemble avec l'atome de carbone adjacent un groupe cyclopentyle ou cyclohexyle.
- 11. Procédé selon la revendication 1, dans lequel R¹ et R² sont, indépendamment l'un de l'autre, un groupe alcoyle en C<sub>1-6</sub>.
- 12. Procédé selon la revendication 1, dans lequel R¹ et R² sont un méthyle.
- 13. Procédé selon la revendication 1, dans lequel R³ est un atome d'hydrogène ou un groupe acyle.
- Procédé selon la revendication 13, dans lequel le groupe acyle est un alcoyle en C<sub>1-6</sub>-carbonyle ou un aryle en C<sub>6-10</sub>-carbonyle.
- 15. Procédé selon la revendication 1, dans lequel R3 est un atome d'hydrogène.
  - 16. Procédé selon la revendication 1, dans lequel X1 est un atome d'hydrogène ou un groupe acyle.

- Procédé selon la revendication 13, dans lequel le groupe acyle est un groupe acyle dérivé d'un acide aminé.
- 18. Procédé selon la revendication 17, dans lequel l'acide aminé est la glycine, l'alanine, l'acide glutamique, la leucine, l'isoleucine, la phénylalanine, l'acide aspartique, la cystéine, la sarcosine, la glutamine, l'asparagine ou la proline.
- 19. Procédé selon la revendication 17, dans lequel l'acide aminé est la glycine, l'acide aspartique, l'asparagine, l'acide glutamique, la glutamine ou la phénylalanine.
  - 20. Procédé selon la revendication 17, dans lequel l'acide aminé est l'acide glutamique ou l'acide aspartique.
  - 21. Procédé selon la revendication 1, dans lequel X2 est un groupe carboxylique qui peut être estérifié.
- 15 22. Procédé selon la revendication 1, dans lequel X<sup>2</sup> est un groupe acyle carboxylique ou carbamique.
  - 23. Procédé selon la revendication 22, dans lequel le groupe acyle carbamique est un groupe aminocarbonyle ou un groupe carboxylique formant un amide avec un acide aminé.
- 24. Procédé selon la revendication 23, dans lequel l'acide aminé est la glycine, l'alanine, l'acide glutamique, la leucine, l'isoleucine, la phénylalanine, l'acide aspartique, la cystéine, la sarcosine, la glutamine, l'asparagine ou la proline.
- 25. Procédé selon la revendication 23, dans lequel l'acide aminé est la glycine, l'acide aspartique, l'asparagine, la phénylalanine, l'acide glutamique ou la glutamine.
  - 26. Procédé selon la revendication 1, dans lequel R¹ et R² sont, indépendamment l'un de l'autre, un groupe alcoyle en C₁-e, phényle ou naphtyle ou R¹ et R² forment ensemble avec l'atome de carbone adjacent un groupe cyclopentyle ou cyclohexyle; R³ est un atome d'hydrogène ou un groupe acyle aromatique en C<sub>e-10</sub>; X¹ est un atome d'hydrogène ou un groupe acyle dérivé d'un acide aminé dans lequel ledit acide aminé est choisi dans le groupe consistant en la glycine, l'acide aspartique, la phénylalanine, l'asparagine, l'acide gluta. mique et la glutamine; X² est un groupe carboxylique, aminocarbonyle ou un groupe carboxylique formant un amide avec un radical d'acide aminé dans lequel ledit acide aminé est choisi dans le groupe consistant en la glycine, l'acide aspartique, la phénylalanine, l'asparagine, l'acide glutamique et la glutamine.
    - 27. Procédé selon la revendication 1, dans lequel le sel est un sel pharmaceutiquement acceptable.
    - 28. Procédé selon la revendication 1, qui est la N-(N-L-γ-glutamyl-D-pénicillamyl)glycine.

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- Procédé selon la revendication 1, dans lequel ledit composé (I) est la N-(N-L-γ-glutamyl-L-pénicillamyl)-L-valine.
  - 30. Procédé selon la revendication 1, dans lequel ledit composé (I) est la N-(N-L-γ-glutamyl-L-pénicillamyl)-L-phénylalanine.
  - **31.** Procédé selon la revendication 1, dans lequel ledit composé (I) est l'acide N-(N-L-γ-glutamyl-L-pénicillamyl)-L-glutamique.
  - **32.** Procédé selon la revendication 1, dans lequel ledit composé (I) est la N-(N-L-γ-glutamyl-D-pénicillamyl)diphénylméthylamine.
    - 33. Composition pharmaceutique propre à être utilisée dans la préparation d'un médicament approprié au traitement curatif ou prophylactique de l'hypertension ou de l'angine de poitrine, qui comprend (a) comme substance active, une quantité efficace d'un composé selon la revendication 1 ou d'un sel de celui-ci et (b) une matière de support, un excipient ou un diluant pharmaceutiquement acceptable pour ce composé.
    - 34. Utilisation d'un composé selon la revendication 1 ou d'un sel de celui-ci pour la préparation d'un médicament pour le traitement thérapeutique d'un mammifère.

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